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THE EFFECT OF IRRITANTS AND DRUGS AFFECTING THE AUTONOMIC NERVOUS SYSTEM UPON THE MUCOSA OF THE NORMAL RECTUM AND RECTOSIGMOID, WITH ESPECIAL REFERENCE TO "MUCOUS COLITIS"

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THIS investigation presents certain observations on the physiologic processes of the rectum and rectosigmoid, which may throw some light on those disorders of the colon apparently concerned with physiologic rather than anatomic abnormality. The changes observed are of two kinds: those affecting the appearance of the mucous membrane as observed through the sigmoidoscope, and those affecting the motility of the rectal wall.

Few studies of the rectal and colonic mucosa in response to the administration of drugs have appeared. Watts and Fulton[1] reported ulcerative lesions of the entire gastrointestinal tract, including the colon, following the production of artificial hypothalamic lesions in monkeys subsequently studied post mortem. The production of experimental gastrointestinal lesions by neurogenic stimulation has also been accomplished in a small percentage of cases by Keller, Hare and d'Amour.[2] These workers produced lesions in the region of the hypothalamus, and found that those cases in which hemorrhage into the ventricle had occurred or in which the lesions had been made in the anterior portion of the hypothalamic area most frequently showed gastrointestinal changes, hyperemia, hemorrhage and erosions. These alterations occurred in all parts of the gastrointestinal tract, including the colon, where the crests of the longitudinal folds showed hyperemia and in some cases frank hemorrhage.

Light, Bishop and Kendall[3] consistently succeeded in producing ulceration of the stomach by the injection of 10 mg. of pilocarpine hydrochloride into the lateral ventricles of rabbits. Other parts of the gastrointestinal tract were not specifically examined. Banting and Hall[4] has in the course of other studies produced gastric ulcers and colonic lesions, probably through overstimulation of the parasympathetic nervous system. Larson and Bargen[5] and Bargen[6] introduced a technic of withdrawing an isolated loop of colon through the anterior abdominal wall. They were thus enabled to study quantitatively changes in mucus formation in the dog. They made studies following the use of different types of cathartics, and in one instance laid the extra-abdominal portion open, so that they could observe the surface in action. They found that the amount of mucus secreted during sleep was at a minimum, and that it was increased after defecation, and still more after defecation stimulated by catharsis. Saline cathartics produced the most normal mucus, castor oil the greatest quantity.

Forsell's[7] barium relief method, which has been applied successfully to gastric roentgen study by Berg,[8] has afforded a third avenue of approach to the study of the mucous membrane of the colon. Knothe,[9] using this technic, made careful observations on the colon in normal and pathologic states, and believes it possible to recognize minimal mucosal changes, such as those seen in "mucous colitis," by this means. He has not, however, published any studies showing the effect of drugs on the colonic mucosa.

The electrically lighted sigmoidoscope affords another and more direct method of approaching the problem. Singer[10] was among the early workers to describe the mucosal changes in mucous colitis which have been subsequently confirmed by other workers,[11] but this method has received little attention as a means of investigating the effect of drugs upon the normal mucosa.

The motility of the colon has been more fully observed. Bayliss and Starling[12] found that stimulation of the wall of the denervated small intestine was followed by contraction immediately above and relaxation immediately below the point of stimulation. He termed this phenomenon the "law of

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the intestine" and believed that it was responsible for the forward movement of intestinal contents. Cannon[13] inferred from these and his own observations that this mechanism was at least partially responsible for the movement of fecal masses in the colon. Hertz[14] also seems to hold this view, stating that the rectum is normally empty, but that when a fecal bolus is allowed to drop into it from the rectosigmoid the defecation reflex is established. Hertz describes a clinical type of constipation, "dyschesia," in which the rectum fills with fecal matter without exciting the defecation reflex, and he is at a loss to explain the syndrome because he finds that all normal rectums are insensible to thermal and painful stimuli. Hines, Lueth and Ivy[15] found in an unselected group of constipated persons that the rectum frequently failed to contract deeply when a balloon was inserted in the ampulla, whereas in the normal controls, deep, painful urges occurred.

SELECTION OF SUBJECTS AND METHOD

In the present study, autonomic stimulating and inhibiting drugs and irritants were applied directly to the mucosa of the rectosigmoid, and in some instances were administered by mouth. The mucous membrane was observed directly.

All the control observations were made on male medical students between the ages of twenty-two and twenty-six. All had essentially normal bowel habits, although 2 had been subject to changes related to emotional strain. One (W.O.L.), a collegiate runner, had had diarrhea for three days before each race and constipation for three days afterward. Another (S.T.) had suffered from emotional constipation. The men were all in good health, and so far as is known were not suffering from any intercurrent disease. A few observations on patients with "mucous colitis" are also reported.

For observation of the colonic and rectal mucosa, an electrically lighted sigmoidoscope was employed. Local applications were administered by small gauze pledgets held in the jaws of a modified bronchoscopic sponge holder. Observations were made after evacuation, and in most cases at nine o'clock in the morning after breakfast, in order to obtain a consistent series of observations. Except where specifically noted, preparatory enemas were avoided. All observations were made with the subjects in the knee-chest position on a well-padded examining table.

The following substances were applied locally on at least two occasions each, in the following concentrations: benzedrine sulfate 1 per cent, epinephrine hydrochloride 0.1 per cent, physostigmine sulfate 1.0 per cent, atropine sulfate 0.5 per cent, pilocarpine hydrochloride 1 per cent, sodium chloride 17 per cent, and oil of turpentine. Acetyl-β-methylcholine chloride was administered by mouth in varying dosages, as were carbaminoylcholine chloride and benzedrine sulfate. The irritant solutions, 17 per cent sodium chloride and turpentine, were kept in tightly stoppered bottles. The solutions of drugs affecting the autonomic nervous system were freshly prepared from tablets or crystals.

During the observation the mucosa was examined at intervals and the following characteristics were particularly noted:

1. The degree of injection, the location in relation to the rectal valves, and to a certain extent the duration of the change were studied.

2. The appearance of mucus, whether as a diffuse, glairy sheen, a frank accumulation of moist secretion or a dried coating partially adherent to the bowel wall, was observed.

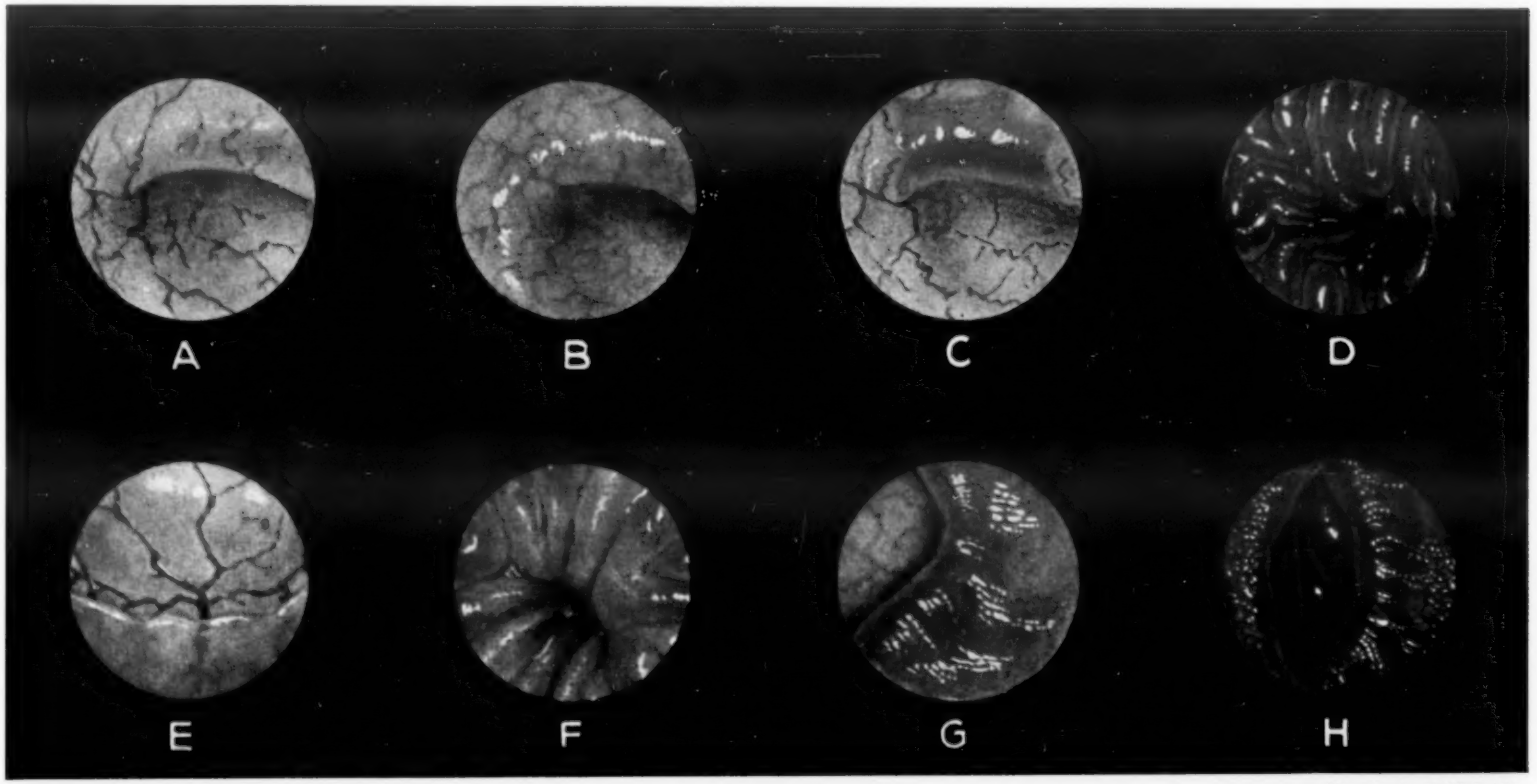
3. Attention was paid to the appearance of the veins and venules, which in some cases were widely engorged and elevated above the surface, but in others were obscured by generalized injection.

4. Granularity and wrinkling of the mucosal surface, probably fundamentally different in their pathological significance, were found to be almost indistinguishable as seen through the sigmoidoscope. In observations upon the normal rectosigmoid it was assumed that roughness of the surface was produced by simple wrinkling of the mucous membrane. In patients with "mucous colitis," however, this distinction was not relied upon.

5. The presence or absence of changes in caliber of the intestine, the appearance or relaxation of spasm and the occurrence of rhythmic activity were observed. When rhythmic activity followed the administration of irritants the exact number of contractions per minute was recorded.

In most cases only one observation was made in a morning. In a few cases irritants were applied at first in the sigmoid and then in the rectum, but owing to the possibility that the physiologic response was due to a summation of stimuli this procedure was discontinued. In a number of cases atropine was applied after cholinergic drugs had been given, and its effect was also observed in patients with rectosigmoid spasm.

Each irritant substance was applied on one occasion in the ampulla of the rectum between the middle and upper valves, and at another time in the sigmoid above the upper rectal valve, usually at the level of the left internal hypogastric artery. Sodium chloride was employed in a concentration of 17 per cent, because such a stock solution was used in the preparation of routine physiological saline and was available in the drug department. It



Drawings by M. McLatchie

PLATE 1

Appearance of Mucosa of Rectosigmoid under Experimental Conditions. A — control observation; B — two hours after standard soapsuds enema; C — immediately after the application of 17 per cent sodium chloride solution locally; D — five minutes after 1 per cent pilocarpine hydrochloride locally; E — five minutes after the local application of 1 per cent physostigmine sulfate; F — fifteen minutes after the local application of 1 per cent physostigmine sulfate; G — after the oral administration of 1000 mg. of acetyl-beta-methylcholine chloride per day for four days. All these observations were made on one subject (E. L. L.) and, with the exception of B, were made without preparation. H — lower sigmoid of a patient with advanced mucous colitis, without preparation. Note the generalized injection, the reduction in caliber and the granular rough surface; sheets of dried tenuous mucus, which were present, do not show in this field. The veins are not dilated at this stage of the disease.

proved to be highly irritant. Oil of turpentine was applied undiluted.

OBSERVATIONS

Below are recorded the observations made after the local administration of drugs to the mucosa of the rectosigmoid. In the case of the purely irritant substances the site of application is noted because of the difference in the response to applications in the rectal ampulla from that resulting from stimulation in the lower sigmoid. In the case of the autonomic stimulating or inhibiting substances, the exact site of application is omitted in the interest of simplicity.

A colored drawing of the appearance of the rectosigmoid mucosa of a normal subject (E.L.L.) who had received no preparation for the examination is recorded in Plate 1*a*. A similar illustration (Plate 1*b*) shows the change in appearance two hours after a standard soapsuds enema (120 cc. of liquid soap dissolved in 2000 cc. of water and administered at 104°F.). A moderate degree of generalized injection, with the appearance of a diffuse, glairy surface, is apparent. In some subjects greater amounts of mucus, even amounting to distinct blobs, appeared. It was interesting to note that the subject just mentioned reacted less strikingly to all forms of stimulation than did some of the others.

Hypertonic salt solution, a 17 per cent solution of sodium chloride, when applied locally for two periods of thirty seconds each, invariably produced a local, circumscribed erythematous area, which soon became covered with a glairy, glistening mucoid secretion. The markings of the veins disappeared in the brilliantly injected center of the lesion. This response is illustrated in Plate 1*c*.

In addition to the local mucosal reaction, hypertonic salt solution appeared to have the property of setting up definite waves of contraction of the musculature of the upper rectum when locally applied at this site. This phenomenon was observed in 8 of 10 subjects. Partial spasm of the rectosigmoid sphincter was noticed in 7 of the 10 individuals. The rate of the peristaltic contraction in the rectal ampulla is recorded graphically in Figure 1. The peristaltic waves so set up are of low amplitude, but for each subject a strikingly characteristic rate is present, a fact which in a number of cases has been confirmed by subsequent stimulation with other substances.

When hypertonic salt solution was applied in the sigmoid above the upper valve, 1 subject, whose peristaltic rate had been 16 per minute on rectal stimulation, showed a rate of only 6 per minute. One other subject showed a few questionable contractions, which were, however, inadequate for counting. In the other cases there was no peristaltic response in this area. The local mucosal reaction was in every respect identical with that produced within the rectum. (See Plate 1*c*.)

In 3 cases *oil of turpentine* was applied locally. A small area of injection was consistently produced, with disappearance of the venular markings. Although this area was somewhat shiny, the exudative, glairy surface seen after the application of salt was absent. In 2 of the 3 subjects stimulation within the rectum produced peristaltic contractions at about the same rate as those produced by salt solution (Fig. 1). In the third case there was no

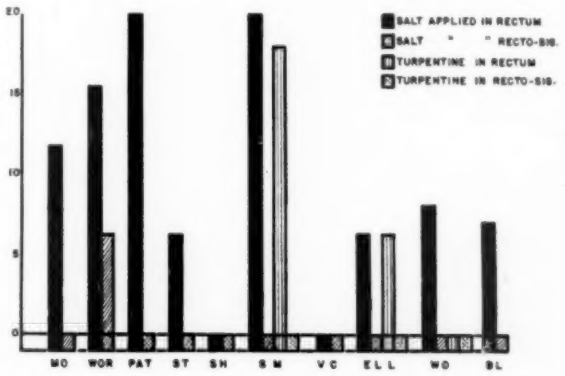


Figure 1. *Differential Irritability of Rectum and Rectosigmoid. Each set of parallel columns represents one subject. The ordinate represents the number of contractions per minute produced by local stimulation with an irritant, which was applied in each instance for two periods of thirty seconds each. Note that in only one instance was any rhythmic activity set up by stimulation above the rectosigmoid valve. Stimulation below this point quite frequently produced reflex contractions.*

peristalsis. In none of the 3 was there any spasm of the rectosigmoid sphincter. When turpentine was applied in the rectosigmoid the usual local mucosal response occurred, but there was no peristaltic activity whatever, and no spasm.

The effect of *epinephrine hydrochloride* in 0.1 per cent solution was investigated in 2 cases. In each it was applied locally twice, for thirty seconds each time. In both instances a local blanched area with a slightly glossy surface was produced. In one of these the application was made in the ampulla of the rectum and was followed by the onset of active peristalsis. In the other it was applied in the rectosigmoid, from which point an acute sharp pain was referred to the umbilicus, but no peristaltic activity ensued.

*Benzedrine sulfate** was applied locally in only 1 control subject, and in a 0.5 per cent concentration was utterly inert. It was also employed in 2 patients with established "mucous colitis," but was

*Furnished through the kindness of Smith, Kline & French Laboratories, Philadelphia.

without effect in relieving spasm or in altering the mucosal picture. Its effect upon the x-ray picture when given in large doses by mouth has been demonstrated by Myerson and Ritvo.[16] In our experience, doses of 20 or 30 mg. given orally failed to produce immediate relaxation in several patients with "mucous colitis." Prolonged oral administration, however, yielded symptomatic relief.

Atropine sulfate, in solutions varying in strength from 0.1 to 0.6 per cent, was applied locally in 12 cases in which spasm was present. Occasionally a moderate degree of spasm of the rectosigmoid valve was found at the time of the initial observation; it was probably due to emotional factors, which are discussed below. Under these circumstances atropine was applied in 4 cases. A 0.1 per cent solution relaxed the sphincter in one case and failed to do so in a second; a 0.3 per cent solution produced relaxation in a third, while in a fourth, a 0.5 per cent solution not only failed to relax the sphincter but in addition produced symptoms of toxicity. In 3 cases, atropine sulfate solutions of strengths varying between 0.1 and 0.6 per cent were at least partially effective in relieving spasm produced by cholinergic drugs. In 5 patients with "mucous colitis," atropine solutions, in concentrations from 0.2 to 0.5 per cent, were successful in 1 case, partially successful in 2, and utterly inert in the remaining 2.

Acetyl-β-methylcholine chloride[17]* in 1 per cent solution, when applied locally in the rectal ampulla, was found in 10 cases to produce a small circumscribed area of injection in all respects similar to that produced by hypertonic saline solution; it had, however, no more dramatic or sustained effect than the latter. In a few cases there occurred peristaltic activity, which was entirely comparable with that produced by saline solution.

Pilocarpine hydrochloride in 1 per cent solution was found to produce very dramatic effects when locally administered in 10 normal subjects. These changes consisted in an immediate bluish-red, almost magenta, injection with a brilliantly glairy mucoid surface. Simultaneously with these changes there appeared a fine wrinkling of the surface of the mucosa, followed by gradual invagination into overlapping folds of tissue. Within five minutes these folds met in the center of the lumen, completely obstructing it with "a squirming spasm." These changes are illustrated in Plate 1*d*. A graphic representation of the changes following the administration of pilocarpine as well as of other drugs is given in Figure 2; this shows the consistency of the findings throughout the entire group of subjects.

Physostigmine sulfate in 0.5 to 1.0 per cent solution was found to produce equally dramatic although less rapid changes, which were consistently demonstrated in the 8 subjects studied. Subsequent to its application (two times for thirty seconds each) the first change occurred in about three to five minutes, when there was a cloudy, diffuse mucosal swelling (Plate 1*e*). The surface was glossy, but injection was usually less prominent than pallor. In some instances there appeared central pallor, with injection about the edges or in traumatized areas. A coarse wrinkling of the surface then developed, and heavy invaginated folds gradually formed. In ten to fifteen minutes they met in the midline and produced the picture of complete spams illustrated in Plate 1*f*.

Acetyl-β-methylcholine chloride was administered by mouth to 10 subjects. In 3 of them (M.O., P.A.T., W.O.R.) 200 mg. was given two hours before the sigmoidoscopic examination. In the other 7 subjects repeated large doses (1000 mg. per day) were given over a longer period of time, and examinations were performed on the mornings of the second and fifth days. In some cases, still larger doses, up to 3000 mg. daily, were subsequently given, but the changes produced were not substantially greater.

In all cases definite mucosal changes took place; these are graphically represented in Figure 2. The changes illustrated in Plate 1*g* are those present in one of the more stable subjects. In general, the changes produced by orally administered acetyl-β-methylcholine chloride consisted in a bluish-red injection most marked between the middle and upper rectal valves. In this area the veins were usually obscured, although they tended to be prominent below the middle and above the upper valves. The surface of the mucosa was finely wrinkled, with the ridges pointing in all directions. This surface was shiny but not glairy. In general, the caliber of the rectum and rectosigmoid was somewhat reduced, although real occluding spasm was present in only 2 cases.

Subjective symptoms were produced in all the patients who took the drug over a period of days, and in 1 who had but a single dose. Five of the men suffered from a tendency toward diarrhea, 1 having associated severe abdominal cramps and 2 uncomfortable low-back pain. Three of the remaining subjects had definite constipation. The other 2, who had only single doses, were symptom free.

Carbaminoylcholine chloride[18]† in doses of .0012 and .0024 mg. daily, was administered by mouth to 2 subjects. The changes produced were essentially the same as those produced by acetyl-β-methylcholine chloride, and consisted of diffuse injection principally between the middle and upper valves,

*Furnished, in the form of Mecholyl, through the kindness of Merck and Company, Rahway, New Jersey.

†Furnished, in the form of Doryl, through the kindness of Dr. Isaac Starr, Jr., Philadelphia, and Merck and Co., Rahway, New Jersey.

prominence of veins in the non-injected areas, a finely wrinkled, glossy surface, and reduction in caliber. The subject who received .0024 mg. daily complained of diarrhea similar to that from which he had suffered after taking acetyl-β-methylcholine chloride. The other subject developed no symptoms at all. A graphic representation of the observed mucosal changes is given in Figure 2.

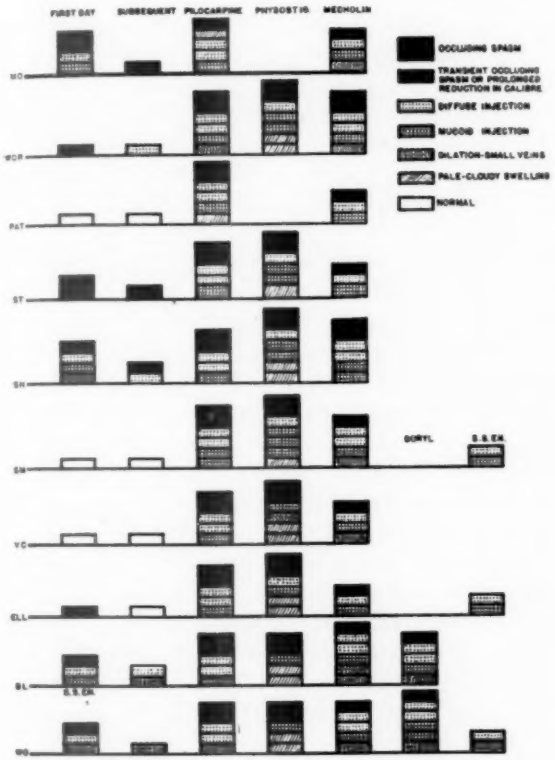


Figure 2. *Schematic Description of Mucosal Appearance. Note consistent changes produced by pilocarpine hydrochloride and physostigmine sulfate locally and by acetyl-β-methylcholine chloride and carbaminoylcholine chloride orally; also the lesser changes produced by soapsuds enemas. Some of the subjects showed changes at the first examination which tended to disappear subsequently. These were attributed to unwarranted apprehension.*

CHANGES NOTED DURING EMOTIONAL STRESS

In the course of these observations it became apparent that a number of the subjects approached their initial examination with a degree of apprehension subsequently proved unwarranted. In tabulating the data it was also noted that in 6 of the 10 subjects the original description of the initial examination revealed changes which were not present to the same degree at the time of introducing the sigmoidoscope on subsequent occasions. In one instance the hospital artist, a woman, noticed a distinct injection of the mucosa when she first examined the subject; in the course of a few minutes it had largely disappeared. No observation was made as to the presence or absence of a simultaneous facial blush.

The degree of difference between the initial observation and characteristic subsequent observations, at the moment of introduction of the sigmoidoscope, is graphically recorded in Figure 2.

DISCUSSION

The changes produced in the mucosa of the rectosigmoid by the administration of cholinergic drugs are akin to those seen in that vague group of disorders best recognized under the term "mucous colitis." Recognized from antiquity, this group of patients was particularly studied by Da Costa[19] in this country and by the dynamically minded European clinicians of the late nineteenth and early twentieth centuries, Nothnagel,[20] Von Noorden,[21] Ewald[22] and others.

The clinical picture of the "mucous colitis" syndrome consists of abdominal pain, usually felt below the umbilicus, and usually related to the ingestion of food or to defecation. Constipated or loose stools of small caliber are generally present and in many cases are streaked with mucus. In some cases there is a generalized abdominal tenderness, most acute in the left lower quadrant, where the sigmoid is usually palpable as a tender, firm mass. In others there are circumscribed attacks of severe colic followed by the passage of long strings of mucus, alternating with periods of comparative comfort. The course of the disease is protracted, with frequent exacerbations and remissions. It usually occurs in tense, nervous persons.

Singer's[10] early description of the rectal and sigmoidoscopic findings in this condition was somewhat amplified by Friedenwald, Feldman, and Rosenthal,[11] who described three stages in its development:

1. Engorgement of vessels; dilation of capillaries; mucous membrane covered with glairy mucus giving a shad-roe appearance.
2. Vessels no longer standing out; glairiness gone, but distinct patches of tenuous mucus present; surface injected.
3. Mucous membrane thinned out, pale, covered with dry mucus; pinhead ulcerations seen when mucus is removed.

In any stage spasm may be present to such a degree as to render the passage of the sigmoidoscope painful. The sigmoidoscopic examination of a patient with mucous colitis is reproduced in Plate 1*h*. The disappearance of vascular prominence, the generalized injection, the absence of glairiness and the presence of patches of tenuous mucus are characteristic of the second stage described by Friedenwald, Feldman and Rosenthal.

Among the early workers to describe the x-ray

changes in "mucous colitis" were Singer and Holzknecht,[23] who called attention to the characteristically reduced caliber of the lower colon. Schwartz[24] again called attention to the reduced caliber of the descending colon and sigmoid, and noticed very sudden occurrence and relaxation of spasm. Discovery of the "string sign," a fine, tenuous shadow supposedly produced by a mixture of barium and mucus in the spastic descending colon, is generally attributed to Crane,[25] while Kantor[26] made observations on the rapid rate of movement of colonic contents in this condition. Knothe[9] applied the barium relief technic to the problem and described a finely wrinkled sigmoid. Von Bergmann and Katsch[27] were successful in demonstrating changes in the caliber of the entire colon in normal individuals following the administration of atropine and pilocarpine — relaxation after the former, marked degrees of spasm after the latter. This observation was a definite contribution to the physiology of the colon, particularly as it is altered in mucous colitis. However, the x-ray findings in the disease have been shown to be extremely inconstant. Spasm, the most constant characteristic reported by Friedenwald, Feldman and Rosenthal,[11] was present in only 51 per cent of the cases, while they reported sigmoidoscopic changes in 89 per cent of 438 cases so examined. The sigmoidoscopic examination in their experience would seem to be of greater significance both theoretically and practically than examination by x-ray. Similarly, the experimental production of mucosal changes by the administration of cholinergic drugs as indicated in the above data seems of greater significance than the production of x-ray changes in tending to confirm the general belief that neurogenic, and probably psychogenic, factors play a significant role in the development of this symptom complex.

The development of constipation or of diarrhea in the subjects who were given large oral doses of acetyl-β-methylcholine chloride and carbaminoylcholine chloride, is of further interest, since these symptoms are commonly experienced in "mucous colitis." In fact, the changes produced by cholinergic drugs have been so strikingly like those seen in "mucous colitis" that we have come to believe the converse to be true; namely, that mucous colitis is the result of some form of overstimulation mediated by the parasympathetic fibers innervating the colon.

The incidental data collected on the difference in irritability of the rectal wall from that of the lower sigmoid (Fig. 1) are suggestive confirmation of the theory of defecation advanced through the work of Bayliss and Starling,[12] Cannon[13] and Hertz;[14] that is, that the passage of fecal matter from the relatively insensitive sigmoid into the more irritable ampulla is the stimulus which normally activates the defecation reflex. This increased reflex irritability is apparently unrelated to subjective pain or temperature sensation, which Hertz has shown to be absent in the normal rectum. It is probable, therefore, that in the type of constipation characterized by rectal retention, — the "dyschesia" of Hertz, — the underlying cause is, as he originally hypothesized, a diminution of the sensitivity of the rectal reflex. That this is probable is also attested by the work of Hines, Lueth and Ivy,[15] who found an absence of deep rectal contractions, as measured by the manometric method, in a group of constipated hospital patients. Unfortunately, they made no effort to classify the type of constipation.

Work is now in progress to determine whether the difference in irritability between the lower sigmoid and the rectum is consistently present in a large series of cases.

SUMMARY

1. The rectal and rectosigmoid mucosa in a group of healthy, young adult males was studied with the aid of a sigmoidoscope.

2. Following the local application of certain irritants, it was noted that the rectum tended to show more reflex activity than the lower sigmoid.

3. After the local application of pilocarpine hydrochloride or physostigmine sulfate, or after the oral administration of acetyl-β-methylcholine chloride or carbaminoylcholine chloride, definite mucosal changes, simulating the sigmoidoscopic picture of "mucous colitis," were produced. All these drugs stimulate or mimic the action of the parasympathetic nervous system.

4. The response to other drugs affecting the autonomic nervous system was investigated.

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THE TREATMENT OF HAY FEVER BY INJECTIONS OF POLLEN EXTRACT EMULSIFIED IN LANOLIN AND OLIVE OIL

A Preliminary Report

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THE injection of pollen extracts into patients with hay fever is one of the most valuable measures available for the treatment of this condition. Despite many improvements in technic and methods since the introduction of this procedure, there are objections to treatment with the solutions of extracts now employed. The large number of injections usually required makes the procedure costly and often inconvenient for the patient. Furthermore, general reactions which may follow an injection are disconcerting and may at times have serious consequences. If the absorption of pollen extract after injection could be made more gradual, it seemed likely that many advantages would result.

Attempts have been made to diminish the rate of absorption and to prolong the effects of therapeutic agents given by injection, but with little practical success.[1] Straus,[2] in 1933, reported good results with the use of emulsions of diphtheria toxoid in lanolin, for immunization against diphtheria.

Studies at the Beth Israel Hospital during the last four years indicate that following the injection of certain dyes and drugs emulsified in anhydrous lanolin and olive oil, the rate of absorption of the substances is diminished and the effects of the drugs are prolonged. Similar emulsions of pollen extracts have been used in treating patients with hay fever. These studies are reported below.

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RATE OF ABSORPTION AND THERAPEUTIC EFFECT

The rates of absorption of phenolsulfonphthalein from water solution and from emulsion in lanolin and oil were compared by determining the rate of excretion of the dye in the urine after injection of each preparation. A stock solution of phenolsulfonphthalein in distilled water containing approximately 100 mg. per cubic centimeter was prepared, using enough sodium hydroxide to effect solution. One part of the stock dye solution was emulsified in 5 parts of lanolin by trituration in a mortar, and 4 parts of olive oil were added, resulting in an emulsion containing approximately 10 mg. of phenolsulfonphthalein per cubic centimeter. A similar 1:10 dilution of the stock dye solution was made in distilled water.* All ingredients were sterilized by autoclaving.

Five patients received 1.0 cc. of each preparation of phenolsulfonphthalein intramuscularly on different days, and the hourly excretion of the dye was measured by the standards used in the renal function test. The average excretion is shown in Figure 1. After injection of the watery solution, 38 per cent was excreted in the first hour. In 4 of the 5 cases, excretion was virtually complete at the end of three hours. After the injection of the emulsion, less than 10 per cent of the dye was excreted in the first hour, and the hourly excretion

during the next seven hours ranged between 10 and 5 per cent. Appreciable amounts of the dye still appeared in the urine eight hours after injection of the emulsion.

That an active drug emulsified in lanolin and oil exerts a more prolonged effect than does a watery solution can be shown by measuring the antidiuretic effect of pitressin when administered in each medium. The preparations compared consisted of pitressin* in water (20 units per cc.) and pitressin emulsified in lanolin and oil (20 units per cc.), made by emulsifying 1 part of pitressin solution (400 units per cc.) in 5 parts of lanolin and 14 parts of olive oil.

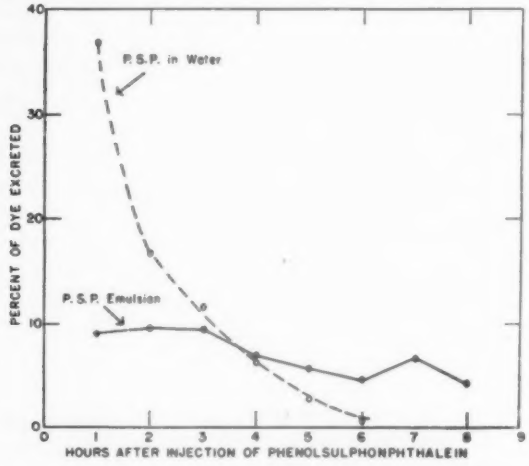

Figure 1. *Average dye excretion per hour in 5 patients injected intramuscularly on different days with the same amount of phenolsulfonphthalein in water solution and in emulsion in lanolin and oil.*

The daily urinary output of a twenty-nine-year-old man with idiopathic diabetes insipidus was measured under four standard conditions: (1) no treatment; (2) surgical pituitrin, 0.5 cc. (10 units), given intramuscularly twice daily; (3) pitressin in water solution, 0.5 cc. (10 units), given intramuscularly twice daily; (4) pitressin emulsified in lanolin and oil, 0.2 cc. (4 units), given intramuscularly once daily. The effect on the urinary output is shown in Figure 2. With no treatment, the daily urinary output varied between 250 and 320 oz. The antidiuretic effect of each injection of surgical pituitrin was so temporary that the daily output was the same as during the control period. The watery solution of pitressin also caused no significant diminution in the daily urinary output. However, when pitressin emulsified in lanolin and oil was given in much smaller doses, the urinary excretion was decreased to about 60 oz., and the antidiuretic effect of each injection was maintained for at least twenty-four hours. Pitressin emulsions in 2 other cases of diabetes insipidus showed similar prolonged effects.

*Pitressin powder supplied by Parke, Davis and Company, Detroit, Michigan.

METHODS

Method of Preparation. A 1:10 ragweed extract was prepared by extracting ragweed pollen with Coca's buffered solution,[3] using 1 gm. of pollen to 10 cc. of solution. On February 27, 1937, a 1:100 pollen-extract emulsion was made by stirring 2 parts of extract into 5 parts of anhydrous lanolin until the entire solution was taken up by the lanolin; 13 parts of olive oil were then mixed in. The mixture was passed through a homogenizer* to make sure of complete emulsification; this step is not essential, however. A 1:500 emulsion was made by diluting the 1:100 emulsion with olive oil. This 1:500 emulsion was used until April 29, 1937, when a more viscous preparation of 1:500 was made by diluting the 1:100 emulsion with 25 per cent lanolin in olive oil. On July 29, 1937, a fresh 1:50 emulsion was made, using 20 cc. of an equal mixture of 1:10 pollen extract and glycerin emulsified in 30 cc. of an equal mixture of lanolin and olive oil. All ingredients and utensils were sterile.

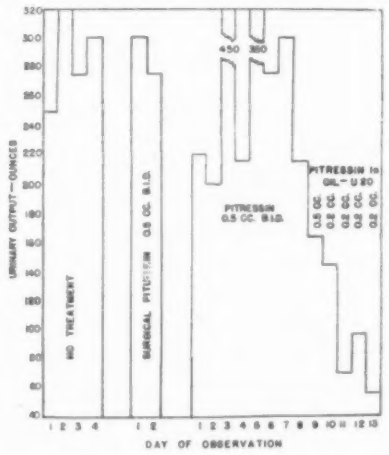

Figure 2. *Daily urine excretion in ounces in a case of diabetes insipidus treated with injections of surgical pituitrin, 0.5 cc. twice a day; pitressin in water, 0.5 cc. twice a day; and pitressin emulsified in lanolin and oil, 0.5 to 0.2 cc. once a day.*

Selection of Cases for Treatment. Two criteria were considered in the selection of cases for treatment; (1) severity of symptoms; (2) degree of sensitivity as shown by the scratch skin test, and the local reactions after the subcutaneous injection of a small dose of ragweed extract. Only patients with moderate to severe symptoms of hay fever were accepted; 3 had asthma in addition to hay fever.

Skin tests in each case were done before treatment by the scratch test method on the forearm,

*Portable hand homogenizer made by Club Aluminum Products Co., Chicago, Illinois.

using dilutions of ragweed extract in Coca's solution in 1:50, 1:500 and 1:5000 dilutions. The maximum reaction to each test, usually after fifteen minutes, was drawn on the record, the description including wheal and erythema; in most instances the test reactions were measured. All the cases had moderate to marked positive reactions to the 1:50 and 1:500 dilutions, and 8 had positive reactions even to the 1:5000 dilution.

Twelve patients had had from one to three subcutaneous injections of ragweed extract, 1:5000 in Coca's solution; 10 had received 0.10 cc., 1 (Case 10) had received 0.05 cc., and 1 (Case 1) had received 0.15 cc. The local reactions which had developed were large in 6 patients (Cases 2, 5, 6, 10, 16 and 17), moderate in 2 (Cases 1 and 15), and small in 4 (Cases 3, 4, 11 and 13). One patient (Case 7) had had no reaction with 0.10 cc. of 1:1000 ragweed extract.

All injections were given subcutaneously in the upper arm with a 26- or 27-gauge needle after the syringe was loaded by using an 18-gauge needle. Because local indurations may develop if injections of lanolin and oil are repeated too frequently in a small area,[4] the sites of injection were varied. No local indurations or infections appeared after any injection given to this group of patients.

Cases 12 and 17 began treatment late and received six and five injections, respectively, before the beginning of the season, the maximum doses being 0.50 cc. of 1:500 and 0.075 cc. of 1:50 emulsion, respectively. In the remaining 15 cases, the maximum dose varied between 0.20 and 0.50 cc. of 1:50 emulsion or its equivalent (Table 1). The number of injections given to attain this maximum varied between seven and twelve, with an average of nine. The maximum dose was repeated at increased intervals with many of the patients until the beginning of the ragweed season. In some cases, doses following the maximum were reduced because of a large local reaction, or because of the approach of the season.

Table 1. *Summary of Treatment with Ragweed-Pollen-Extract Emulsion.*

Case No.	Age	Duration of Disease	Preseasonal Treatment in 1936	First Treatment with Ragweed Emulsion		Maximum Dose Administered			Number of Injections to Attain Maximum Dose	Number of Injections up to Aug. 13	Number of Injections during Ragweed Season	Total Number of Injections	Clinical Results
				Date	Dose of 1:500 dil.	Date	Dose						
	yr.	yr.		1937	cc.	1937	dil.	cc.					
1*	38	15	0	4/12	0.15	6/21	1:100	0.50	9	12	1	13	Good
2	16	3	0	3/29	0.10	8/6	1:50	0.50	11	13	0	13	Excellent
3	16	3	0	3/29	0.10	7/12	1:100	0.50	10	12	1	13	Good
4	25	2	0	4/12	0.10	6/18	1:100	0.50	8	11	1	12	Good
5	23	4	Sol.	4/23	0.10	6/18	1:100	0.50	8	12	1	13	Good
6	15	2	0	4/23	0.10	6/28	1:100	0.50	9	12	0	12	Excellent
7	59	33	Sol.	4/26	0.10	8/9	1:50	0.40	8	10	0	10	Good
8*	42	15	Emul.	4/30	0.10	8/6	1:50	0.50	9	11	3	14	Good
9	42	6	0	5/10	0.10	8/9	1:50	0.20	12	13	4	17	Good
10	42	7	0	5/10	0.10	8/2	1:50	0.25	10	11	1	12	Excellent
11	22	5	Sol.	4/26	0.10	8/6	1:50	0.35	9	12	0	12	Excellent
12	31	2	0	7/26	0.10	8/13	1:500	0.50	6	6	2	8	Fair
13	25	3	Sol.	6/4	0.10	8/13	1:50	0.45	10	10	1	11	Good
14*	19	15	Emul.	6/11	0.05	8/9	1:50	0.20	8	8	3	11	Good
15	45	12	0	7/2	0.10	7/30	1:50	0.25	7	10	1	11	Good
16	16	2	0	7/2	0.10	8/6	1:50	0.45	10	11	0	11	Excellent
17	17	7	0	7/26	0.10	8/9	1:50	0.075	5	5	1	6	Fair

*Asthma in addition to hay fever.

Method of Treatment. The initial dose was 0.10 cc. of 1:500 emulsion with the exception of 2 cases which began with 0.15 cc. (Case 1) and 0.05 cc. (Case 14). The subsequent doses were increased at weekly intervals according to the local reactions until the maximum dose was reached. If this amount was reached long before mid-August, as in cases started on treatment early in the year, the maximum dose was repeated at intervals of two to four weeks. Four patients (Cases 12, 15, 16 and 17) who began treatment in July were given two injections a week until the beginning of the ragweed season, about August 13. Up to July 29, the maximum dose was 0.50 cc. of the 1:100 preparation. This was made on February 27, and since it was five months old and had possibly deteriorated, a fresh 1:50 emulsion was made on July 29, which was used with some patients, the maximum dose being 0.50 cc.

The season is considered to extend to the end of September. The doses given during the season were less than the maximum dose reached before it began.

RESULTS

Local and General Reactions. To determine whether pollen-extract emulsion was more slowly absorbed than the solution in water, 10 patients were injected at the same time with a 1:5000 solution into one arm and a 1:500 emulsion into the other. The amount usually injected was 0.10 cc. The size of the reaction produced by each injection was observed up to one hour. Invariably, the

emulsion produced a smaller immediate local reaction than the solution, even though it contained ten times the amount of pollen extract. After several hours, however, the local reaction from the emulsion approached that from the solution, and often became larger and lasted longer. This indicates that absorption of the pollen extract from the emulsion was delayed.

Three patients had general reactions. In Case 14 the patient received 0.10 cc. of 1:50 emulsion on August 2 and 0.20 cc. on August 9. Five minutes after the last injection he developed a large local reaction, accompanied by wheezing. He responded quickly to 0.50 cc. of 1:1000 adrenalin, and no tourniquet was necessary. In Case 15 the patient received 0.35 cc. of 1:100 emulsion on July 23. A week later he was given 0.25 cc. of 1:50 emulsion, and about five minutes later developed wheezing which did not require treatment. The following day the local reaction was "larger than usual." In Case 17 the patient received 0.50 cc. of 1:500 emulsion on August 6. Three days later she was given 0.075 cc. of 1:50 emulsion. About thirty minutes after injection, while on her way home, she developed a large local reaction and a "wheezy feeling" which persisted until the next day. She did not call a physician.

All three of these general reactions occurred after the patients had been given a freshly made 1:50 preparation, the preceding injections having consisted of material five months old which had probably deteriorated to some degree. The reactions were mild, and did not resemble the acute, dramatic, general reactions occasionally seen with the usual ragweed solutions.

Effect on Skin Reactions. Each case was skin-tested before treatment. At intervals thereafter the scratch tests were repeated and changes were noted. In every instance there was a striking progressive diminution in the size of the reaction. Before treatment, every patient showed moderate to marked reactions to the 1:50 and 1:500 dilutions, and 8 showed slight to moderate reactions to the 1:5000 dilution. After treatment, no patient reacted to the 1:5000 dilution; 5 showed questionable to slight reactions to the 1:500 dilution and 12 showed negative ones; 13 showed slight to moderate reactions to the 1:50 dilution and 4 showed virtually negative ones. For example, the patient in Case 10, who gave the most pronounced reaction to the skin test before treatment, showed the following wheals on repeated testing:

		1:50 DIL.	1:500 DIL.	1:5000 DIL.
		mm.	*mm.*	
Before treatment	April 30	55 x 38	38 x 14	Small
After treatment	August 16	8 x 8	None	None
	October 18	6 x 6	None	None

The patient in Case 17, who had the smallest number of injections, showed the following wheals:

		1:50 DIL.	1:500 DIL.	1:5000 DIL.
		mm.	*mm.*	
Before treatment	July 26	18 x 18	5 x 5	None
After treatment	August 16	10 x 10	None	None

To determine whether the tolerance to ragweed extract was increased by treatment with emulsion, 8 patients after reaching a dose of 0.40 or 0.50 cc. of 1:100 emulsion were injected with 0.10 cc. of 1:100 ragweed solution. The reactions produced ranged from negative to very slight.

Clinical Results. The evaluation of results in the treatment of hay fever is difficult. After treatment, one patient may have more symptoms than another, yet show more improvement. Also, some patients complain more than do others whose symptoms are more severe. With these considerations in mind, the patients have been grouped according to clinical results in three arbitrary divisions.

Excellent Results: This group comprises 5 patients (Cases 2, 6, 10, 11 and 16) who had no days of discomfort during the entire season. On close questioning, they admitted that on arising they occasionally had some stuffiness in the nose and slight sneezing which lasted only a short time, with no discomfort during the remainder of the day or night. No symptomatic treatment was required in this group. Four patients had no injections after the season started, and 1 (Case 10) had one.

Good Results: This group includes 10 patients (Cases 1, 3, 4, 5, 7, 8, 9, 13, 14 and 15) who had mild symptoms of hay fever during the day on four or five occasions during the season, but did not require active symptomatic treatment. In comparison with years in which they had had no treatment, the degree of relief was marked. No patient was incapacitated at any time. The 3 patients who had asthma in addition to hay fever had much less discomfort than in other years, and the wheezing was readily controlled by ephedrine sulfate, 3/8 gr. Only 3 of the 10 patients received more than one injection during the season.

Fair Results: Two patients (Cases 12 and 17) who reported for treatment late in July, and received only six and five injections, respectively, before the onset of the season, had more symptoms than the other patients in this series. They were, however, definitely better than in previous years in which they had received no treatment.

DISCUSSION

Microscopic examination of an emulsion of water in lanolin and oil shows the watery phase as minute droplets surrounded by lanolin and oil. When such an emulsion is injected, each droplet must be

liberated from its envelope before it can come in contact with the tissues and be absorbed. The same amount of water if not emulsified can be absorbed much more quickly, as shown by a comparison of phenolsulfonphthalein excretion from solution and from emulsion (Fig. 1). In the same way, an active drug when emulsified has a prolonged absorption and prolonged action. As indicated in Figure 2, 4 units of emulsified pitressin once a day had a prolonged antidiuretic effect sufficient to control a case of diabetes insipidus for at least twenty-four hours, whereas 10 units in solution given twice a day had so temporary an effect that the twenty-four-hour urinary excretion was the same as when no treatment was given. This technic has been applied to other active drugs.[4] Several patients with bronchial asthma have had longer periods of relief between attacks when emulsified adrenalin was used than when adrenalin in 1:1000 solution was given. In fasting rabbits, emulsified insulin produced hypoglycemia lasting eight hours or more as compared with three hours when the same amount of insulin was given in solution.

Delay in the absorption of emulsified pollen extract is indicated by the fact that milder immediate local reactions were produced by injections of emulsified extract than by those of watery solutions, even when the amount of extract in the emulsion was ten to twenty times as great as that in the solution. The value of this method of delayed absorption in the treatment of hay fever may be determined by comparing the results in this series with those obtained by treatment with extracts usually used. When pollen extract in water solution is injected into a sensitive patient, the entire amount comes into immediate contact with the antibodies in the tissues and the maximum reaction starts immediately. With emulsion, however, only part of the extract comes into immediate contact with the antibodies, the remainder being slowly released. Because of this, a larger amount of pollen extract may be given in emulsion. The patients in this series were all started on treatment with a 1:500 dilution, whereas the usual initial dose of pollen extract in patients with the degree of sensitivity manifest in this group is a 1:5000 or weaker dilution.[3, 5, 6] Since larger doses may be given, a specified maximum dose can be reached with fewer injections. The maximum dose aimed at is usually 0.50 cc. of a 1:100 or 1:50 dilution of extract, requiring from fifteen to twenty-five injections of the extract in solution. This dose was reached in this series by from seven to twelve injections of emulsified extract with an average of nine, approximately half the number usually required. Furthermore, if the data in 4 cases treated in 1936 with ragweed solution and in 1937 with emulsion (Table 2) are compared, it is evident that fewer injections of emulsion resulted in a higher maximum dose. The decrease in the number of injections reduces the expense and inconvenience to the patient, so that more patients with hay fever will find it possible to take treatment. Since the time necessary for preseasonal treatment is shortened, patients starting treatment late have more chance of getting good results. In cases reporting after the onset of the season, it is also possible that treatment with emulsions may be more effective than treatment with watery solutions. In using emulsions of lanolin and oil, care must be exercised to avoid injecting too frequently into the same area. Several patients who injected themselves at home with pitressin or adrenalin emulsions developed temporary local indurations which were apparently due to neglect of this precaution. A few instances of minor local infection also occurred after self-administered emulsions. No injection of emulsion given by us has caused any local complications, and none were encountered in this series. The injections are painless except for the needle puncture.

Table 2. *Comparison of Treatment and of Results in 4 Cases of Ragweed Hay Fever Treated in 1936 with Ragweed Extract in Solution and in 1937 with Ragweed Extract in Emulsion.*

Case No.	Treatment	Maximum Dose		Number of Injections	Clinical Results
		dil.	*cc.*		
5	Sol.	1:500	0.40	11	Poor
	Emul.	1:100	0.50	8	Good
7	Sol.	1:100	0.70	16	Good
	Emul.	1:50	0.40	8	Good
11	Sol.	1:100	0.25	19	Poor
	Emul.	1:50	0.35	9	Excellent
13	Sol.	1:100	0.05	9	——*
	Emul.	1:50	0.45	10	Good

*This patient received no injections between July 24 and September 4, 1936, so that the results obtained in that year are not considered comparable.

The effect on the sensitivity as indicated by skin tests is of interest. The ability of treatment with pollen extracts to affect the skin sensitivity has been open to question; a definite decrease in the size of skin tests as determined by the scratch method, however, has been demonstrated in some cases following treatment.[7] All the patients in this series showed marked reduction in the size of the skin tests. It seems likely that the slow absorption from emulsion permits the extract to act over a longer period of time, and thereby to serve as a better desensitizing agent, than is the case with the extract in solution. It is possible, therefore, that this method may result in a higher percentage of cures than that now obtained. Also, the greater desensitization may make it possible to increase the intervals between injections in the perennial form of treatment.

The danger of general reactions is everpresent, and may have serious consequences.[8] To avoid these severe immediate anaphylactic reactions, the application of a tourniquet proximal to the site of the injection and the addition of adrenalin to the pollen extract have been advised, in order to delay the absorption of the pollen.[9] These precautions are not sufficiently observed, unfortunately, because of their inconvenience. Although adrenalin may slow the absorption of pollen extract from the site of injection, the entire amount of pollen does come in immediate contact with the tissues, and if the reaction is violent enough, a general reaction may occur. With the use of emulsions, where only a part of the pollen extract reaches the tissues at any one time, it is reasonable to suppose that the tendency to severe general reactions will be greatly reduced, especially if the methods now advised are used.

The clinical results obtained in these cases were very satisfactory. There were no failures in treatment; even the 2 patients whose treatments started late and who received only five or six injections had at least fair results. Of the remaining cases, 5 had excellent results and 10 good results. There is reason to believe an even higher percentage of excellent results may be obtained by larger dosage and more treatment during the pollen season. The results compare favorably with those obtained from the usual treatment with solutions,[3, 5, 6] and in the cases of this series which were treated in 1936 with solutions, the results with emulsions were definitely better.

The advantages of pollen-extract emulsions as compared with the solutions now used seem apparent, and the findings in this series are significant. The results warrant a more general application of this method.

SUMMARY AND CONCLUSIONS

A method is described for emulsifying water solutions of drugs in anhydrous lanolin and olive oil. Evidence is presented that such drugs when injected are more slowly absorbed, have a more prolonged action, and are therefore more effective than when administered in water solution without emulsification. Emulsions of ragweed pollen extract were utilized in the preseasonal treatment of 17 patients with moderate to severe symptoms of hay fever and moderate to marked sensitivity to ragweed pollen.

In comparison with the treatment of such patients by pollen extracts in solution as now used, certain advantages of the emulsions are apparent:

1. Pollen extracts in emulsion are more slowly absorbed. Ten times as much pollen extract in emulsion produced less immediate local reaction than the solution.

2. Larger doses may be given. The patients in this series received an initial dose approximately ten times as great as usual.

3. The number of injections necessary to reach the usual maximum dose of 0.50 cc. of a 1:100 or 1:50 dilution is reduced. This dose was reached in an average of nine injections, about half the number usually required with the solutions now in general use.

4. Sensitivity as indicated by skin tests is markedly reduced.

5. The tendency to severe general reactions is decreased because of the slow absorption of the extract.

6. The clinical results are as good or better with the extract in emulsion than with the extract in solution. There were no failures. Two patients who started treatment late and failed to reach the usual maximum dose had fair results. Of the remainder, 10 had good results, and 5 had excellent results.

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THE ADRENOGENITAL SYNDROME AND ADRENOCORTICAL TUMORS

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DYSFUNCTIONS of endocrine glands produce, at times, changes in metabolism and in physical characteristics. Certain such changes belonging in the sexual sphere have been described as the adrenogenital syndrome, and have been shown to be caused in some cases by a tumor in the adrenal cortex. On the other hand, tumors of the adrenal cortex have occurred without producing any recognized endocrine change. Again, somewhat similar syndromes have developed with tumors of other glands,—the pituitary, pineal, thymus, testis or ovary,—or without demonstrable glandular tumors. So that the only information as yet available relates to part of the mechanics involved in the dysfunction.

There have been under observation since 1927 at the Squier Clinic 35 cases of adrenocortical disturbances, 8 male and 27 female. Some showed syndromes due to adrenal tumors, but in others no such tumor could be proved. Certain other cases had adrenal tumors but no endocrine dysfunction. A discussion of this complex problem as seen in this series may be of interest.

SYMPTOMS

Corticoadrenal tumors may exist with or without the adrenogenital syndrome. When the syndrome is present the endocrine changes appear to follow three more or less separate paths. The most frequent change is the development of the secondary sexual characteristics of adult masculinity, and is best termed androtropic; secondly, evidences of maturity may occur in the young and those of an even more advanced age in the mature; thirdly, there may be changes in metabolism affecting mostly the plasma, the fat distribution, the skin and the psychologic balance. The symptoms of this syndrome vary according to the sex and age of the patient and the degree of malignancy of the tumor. Since similar syndromes occur without demonstrable tumor, a review of the symptoms, with a discussion of their divergence in tumor and non-tumor cases, may give the clearest picture that can be shown at present in these unusual clinical states.

When the tumor occurs in the male before puberty, precocious sex development is the most frequent symptom. Associated with this phenomenon there is an increase in muscular development which produces in some individuals the so-called Herculean type. This condition, according to Harris and Plewes,[1] characterizes over 60 per cent of the collected cases. There is often a proportionate increase in athletic ability. In addition, a premature growth of hair occurs on the genitals, face, body and extremities, and the hair is frequently coarse and dark. The genitals enlarge and become adult in type. Coinciding with this precocious development, substances with male hormone properties appear in the urine, although according to Womack and Koch[2] most boys under ten do not excrete demonstrable amounts of male hormone. Rapid growth takes place but is followed by cartilage loss with cessation of growth, so that the subject may actually become much shorter than children of the same age. The dentition is advanced. A certain number of subjects develop obesity, most marked in the face and trunk, and redness of the face. Skin changes such as acne occur as at puberty. Precocious tastes and appetites, including sexual desire, may develop. Frequently, children show mental development beyond the age index.

Similar endocrine changes, described as macrogenitosomia præcox, have occurred with tumors of the pineal gland. An interesting group of cases with similar sexual symptoms without evidence of tumor, occurring in one family, was classified by Rush and his co-workers[3] as primary, primary constitutional, or congenital pubertas praecox. He believed that such a condition was determined genetically. We studied 4 male children with macrogenitosomia praecox. The first child, aged five, with premature puberty, showed no abnormal change in his pineal, pituitary, thymus, gonadal or adrenal glands by x-ray or otherwise, so that a cause for the endocrine abnormality could not be demonstrated. The second boy, aged seven, was sexually mature and had the height and weight of an eleven-year-old. There were also epiphyseal changes corresponding to those of twelve or over. There were no changes from normal in the pineal gland, pituitary, thymus and gonads. Air injection and x-ray revealed a left adrenal gland enlarged to about one third the size of the kidney, and an apparently normal one on the right. This enlarge-

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ment is suggestive of increased adrenocortical function as the cause of sexual maturity, and implies the presence of male hormone in the urine, but whether the latter is due to hyperplasia or tumor of the gland awaits operative confirmation. The third boy, aged eleven, previously described,[1] had marked hirsutism and hypertrophy of the genitals. The early fusion of the epiphyses, with apparent shortening of the extremities, and the continued facial and muscular growth suggested an achondrodystrophic dwarf. At the time of this boy's hospitalization we were able to show the presence of female hormones in his urine, but no facilities were then available for determining the excretion of male hormone. Air injection and x-rays of the adrenals showed a change in one which indicated hypertrophy or tumor, but the mother's failure to co-operate prevented further study. The long-standing symptoms, seven or eight years in duration, with the only demonstrable anatomic glandular changes in one of the adrenals, suggest an adenoma or hyperplasia of the cortex as the causative agent. In the fourth case, also a boy of eleven, the symptoms had been present since infancy, again suggesting an achondrodystrophic dwarf with marked hirsutism and hypertrophied genitals. Although this case closely resembled the foregoing one, x-ray studies disclosed no anatomic changes in the endocrine glands. In neither of these cases was there any evidence of a hereditary or familial occurrence.

Thus of the 4 male children with adrenogenital syndrome, 2 showed anatomic adrenal changes that were suggestive of but not operatively proved to be the cause of the symptoms, while in the other 2 the syndrome had existed for relatively long periods without any causative anatomic glandular change's being demonstrable.

In the male after puberty, adrenocortical tumors have occurred without producing any endocrine changes (Hartman,[5] Stevens,[6] Gibson[7] and others). Such a case was previously described[1] in which autopsy revealed a carcinoma of the right adrenal cortex with extensive metastases. A second patient, a male of thirty-six, was without symptoms except for pain in his left flank. A tumor of the left adrenal was shown by air injection and x-ray. On removal it was found to have arisen from the lower portion of the adrenal and to have grown in front of the kidney, without causing its displacement. Microscopic section showed that the tumor was derived from the adrenal cortex, but it was impossible to tell from which cell structure.

Adult males with adrenocortical tumors and evident endocrine changes have been reported. Macera[8] described a case with adiposity, polydipsia, hypertrophy of the genitals, changes of metabolism and increase of secondary male sexual characteristics. Long and Gray[9] reported an adrenocortical tumor in a male acromegalic. However, such changes as occur have been mostly toward feminization, best termed gynecotropic. Among such cases Weber[10] cited 2 from the literature with hypertrophy of the mammae and atrophy of the testes, both having adrenocortical tumors. More recently Holl[11] and Lisser[12] have each described cases of feminization of the male with such tumors. One male adult in our series had obesity, atrophy of the genitals, and a marked increase in hair. Besides the decrease in the size of the testes, the only demonstrable glandular change was an enlargement of both adrenals, shown clearly by air injection and x-ray. No operative procedures to establish the cause of the adrenal hypertrophy were permitted, and no hormonal studies were made.

In the female, when the disease occurs before birth or in early infancy, only cases of tumor with definite hormonal changes have been reported, and the symptoms have been best described as pseudohermaphroditic. It has been suggested that all cases of pseudo-hermaphroditism are the result of hypersecretion of the adrenal cortex. Yet the only adrenal lesions known to produce such changes are cortical tumors. Young[13] has most interestingly described his experiences in correcting these defects, and has discussed their association with adrenal changes. The contention that such changes occurring in the secondary sex organs are due to hormonal influences, possibly apart from tumor, has received much support from the experimental work of Hain,[14] who has shown that hypospadias in the female offspring of the rat may be produced by the injection of the female sex hormone (estrone) before or immediately after birth. Moreover, Greene and Ivy[15] have demonstrated that male sex hormone (testosterone) when injected early in pregnancy in rats produces an arrest in the development of the vagina and a hypertrophy of the clitoris to the point of resembling a penis, or results in intersexuality (freemartin). If a tumor develops in the female before puberty and is highly malignant, death may occur before any marked changes take place. Usually the characteristic tendency toward adult masculinity is noted. This is first shown by hair growth which is masculine in its distribution. The genitals change, the clitoris increasing in size until it resembles a penis. The labia majora enlarge and become deep red. These patients, as a rule, do not menstruate even though the age of puberty has been reached. Two exceptions have been reported (Bulloch and Sequeira,[16] and Cecil[17]). The voice is often deep and husky. Complete dentition and union of the

epiphyses occur, as in the syndrome in male children. There may be obesity of the face, neck and trunk, with an increase in the size of the mammary glands. The skin may become coarse and dry, and acne may develop.

In the female after puberty and before the menopause, symptoms of the adrenogenital syndrome are more frequent — 27 of our 35 cases were in this category. Of these, only 6 had proved tumors of the adrenal cortex. Adrenocortical tumors may also occur without any endocrine syndrome in the female, as shown by 1 of our patients who had a tumor on the left side, with cells mostly resembling the zona fasciculata. The changes produced tend toward the secondary sex characteristics of masculinity (androtropic). More rapid aging and metabolic changes of plasma, fat and skin, which are similar to those described in younger females, take place. These androtropic changes are accompanied by a suppression of the female characteristics. The first symptoms are amenorrhea and hirsutism. At the beginning there may have been scanty menstruation, followed by its complete cessation, lasting until the tumor is removed. Headaches have frequently occurred at the time when menstruation should have taken place. Associated with the absence of menstruation there is often complete loss of sexual desire and libido. Homosexual desires have been reported by Holmes,[18] with a return to normal after removal of the tumor. All our tumor cases had little or no sex thoughts, and none exhibited any homosexual trend. The menses in these cases started after the tumors were removed, sex attraction and libido returning at the same time. In 1 case metastases developed later and the menses again ceased, as did the libido.

Increase in hair or hirsutism occurred early. The pubic escutcheon became masculine in shape, and hair appeared on the face, chest, back and extremities. The hair was black and coarse, except in 1 case. A loss of head hair was also noted, 1 woman becoming bald. The growth of hair on the body may become extraordinarily profuse, especially about the genitals. On removal of the tumor the hair falls out, chiefly at the time of menstruation and frequently while bathing. In women who have shaved, the loss of hair on the face has been disappointingly slow after operation. One woman was still shaving every other day three years after removal of the tumor.

The changes in the sex organs are more marked the younger the subject. The clitoris may resemble a penis, and the labia majora become hypertrophied and reddened. In older women there has been a definite loss of ovarian tenderness on pelvic examination. At operation in all the tumor cases, the ovaries have been extremely small and the uterus has been smaller than normal. In young subjects the breasts may resemble a boy's, but female development follows removal of the tumor. In older subjects there may be a reduction in size, with a return to normal after operation. The voice becomes deeper and more masculine the earlier the disease occurs in youth. This has been shown to be due to a marked increase in the length of the vocal cords.

With masculinization, rapid maturity, with cessation of growth and absorption of the epiphyseal cartilages, occurs in younger individuals. Older people appear to be of more advanced age than is the case. Apparently these women are not fertile during the symptomatic period of the disease, although 2 had had children before the onset of symptoms. Marked sexual changes in 1 case were not accompanied by any pronounced changes in the metabolism of plasma, fat deposits or the skin.

Metabolic changes associated with the masculinization of the individual take place more frequently, although cases have been seen in which the latter was slight and the former were marked. With these changes the skin becomes dry and coarse, and acne frequently develops. Redness and duskiness of the face and hands were marked in 2 cases. Both patients had polycythemia, one with a red-cell count of 5,700,000 and the other with one of 6,300,000, and each with a hemoglobin of 125 per cent. In 1 case the total blood volume was about 50 per cent of normal. Similar duskiness with increased red-cell counts has been described in cases of Cushing's basophilic adenoma of the pituitary, but no records of blood volume have been made. The paralleling of the symptoms and blood changes suggests that the basic mechanics of the plasma changes in these conditions may be somewhat the same, since in Cushing's syndrome additional adrenal changes have frequently been found at autopsy. Pigmentation may take place. Striae atrophicae of the skin of the abdomen and thighs, similar to that described in Cushing's syndrome, also occur. Obesity is frequent with such changes and is restricted to the face, neck and trunk. With the more malignant tumors it is replaced by emaciation. Edema of the face, feet and hands seems also to be associated with the more rapidly growing tumors. Not infrequently shortness of breath, weakness and cardiac palpitation accompany the edema. Symptoms referable to hypertension are frequent, and hypertension of a moderate type, varying from 138 to 195 systolic, has developed in tumor cases. It was uniformly lower in the cases with marked sex changes, and higher in those with obesity and plasma changes.

The mental alterations in these patients are at times pronounced. They are emotional, and some are very depressed. All our patients were somewhat difficult to handle while in the hospital. In 1 case the emotional change was more pronounced than the physical. After the cessation of her menses the patient developed a marked inversion-depression psychosis in which she did not speak voluntarily for almost two years. She showed obesity of Cushing's type, duskiness of the hands and face, polycythemia, and slight hirsutism and amenorrhea, but there was little change in the clitoris. No male sex hormone could be demonstrated in her urine. A tumor of the left adrenal was shown by air injection and x-ray. Immediately following its removal she spoke rationally, acted in a normal manner and chatted with her husband and family, and apparently resumed her normal interest in her surroundings. Such a change upon the removal of a hormonal tumor is of extraordinary interest from the point of view of its possible mechanics. The emotional changes in other cases were just as evident but much less marked.

The basal metabolic rates showed such a variation that they could only be interpreted in relation to the general state and not in specific relation to the adrenal situation. Chemical analyses of the blood showed no particular change, except that in some cases the cholesterol content was high. There was no demonstrable change in the blood chloride, sodium or potassium. Two tumor cases showed a low sugar tolerance, and in addition metabolic and plasma changes, obesity and edema. An autopsy in 1 of these cases showed a normal pituitary gland and pancreas.

The 20 cases of women without demonstrable tumor presented a varying number of the symptoms of the adrenogenital syndrome (Broster and Vines[19]): hypertrichosis of the male type; menstrual dysfunction; changes in the body contour; changes in the genitalia; changes in the larynx; and changes in the psychologic outlook. Since these symptoms are also those produced by cortical tumors, a differential diagnosis in some cases is difficult without visualization of the adrenal. All in all, the changes in the cases without tumor were less pronounced and more varied than those in the tumor cases.

The changes in menstruation varied. In several the amenorrhea was primary, menstruation never having taken place. More frequently menstruation was scanty, infrequent or irregular, in contrast to the tumor cases, where complete cessation was the rule. On the other hand, some of the non-tumor cases had little change from normal. These patients did not complain of headache or nervous, suppressed catamenial periods as did those with tumor. Not infrequently in some of the older cases there was a long history of symptoms — ten or twenty years — with little acceleration, a duration most unusual in tumor.

The hypertrichosis in the non-tumor cases was varied. In some it was of a moderate growth, but in a few it was extraordinarily profuse. The head hair, however, more uniformly kept its normal color. No tendency to baldness was seen. The hair of the body and face was coarse, but not so uniformly coarse and dark as in the tumor cases.

Changes occurred in the sex organs in 12 cases. These were an enlargement of the clitoris and an increase in the size of the labia. The breasts were undeveloped in 11 cases; in the remaining 9 they were apparently normal. At operation these cases did not show the uniformly small, contracted ovaries seen with tumors. Two had cystic ovaries, neither of which showed any masculinizing cells on section.

Obesity was present in 8 of the non-tumor cases. The most pronounced was that of a girl of 20 who weighed 365 lb. She looked at least thirty-five years old. The obesity was of a generalized type. The body contour apparently varied with the age and onset of virilism. The younger female patients resembled boys, but the older ones were feminine in appearance. Seven had male figures; there were 3 long, bony individuals who had both male and female characteristics. The voices were deeper than normal females only in those cases in which hirsutism had begun in early youth. Of the skin changes, dryness and acne were infrequent, and duskiness of the hands and face did not appear.

Emotional instability as a whole was less marked among the non-tumor cases. A few were difficult to control, because of a predominating fear of harm. Normal sex attraction with a feminine psychology was present in most. A frequent complaint was depression because of apparent lack of sex appeal.

A definite loss or lack of fecundity seems to be associated with the adrenogenital syndrome, children being unusual among those who marry. In addition, a certain hereditary or familial influence is present in some non-tumor hirsutisms. This syndrome occurred three times in sisters, and 1 of these had a cousin and two paternal aunts with the same changes. Although the comparison is only suggested, these patients often seem to resemble the animals, produced experimentally, which have been described as intersexuals or freemartins. There were no twins in any case, but there is experimental evidence showing that some hormonal influence besides that of a male twin may produce such conditions.

DIAGNOSIS

In cases of adrenal tumor without endocrine syndrome, the most frequent symptom has been pain in the side involved. The tumors as a rule have been large and often palpable in the region of the kidney, which they displace downward. This can be shown by x-ray photographs and pyelograms. As has often been stressed, the upper pole of the kidney is moved so that the hilum faces downward, a position that does not occur in ptosis or in renal ectopia. In some cases actual invasion of the kidney has given irregular compression shadows of the pyelographic media similar to those produced by renal tumors.

When the adrenogenital syndrome is present the diagnosis lies first between a possible tumor of the pineal gland, pituitary, thymus, ovary or adrenal gland. When the presence of a tumor cannot be established, increased activity of certain glands has been suggested as a cause. This activity is frequently assigned to the adrenal cortex. When a glandular tumor is present there appears to be some variation of symptoms in accordance with the gland involved. The hirsutism of pituitary dysfunction has been described as the silky, lanugo type, and the facial growth predominates on the cheeks. Hirsutism due to ovarian growth is more universal, somewhat masculine but often scanty. When the growth is due to involvement of the adrenal it is characterized by coarseness, darkness and wide distribution, being present on the lips and chin. The types of obesity in these glandular disturbances are somewhat variable. Pituitary obesity has been characterized as of the girdle type, ovarian obesity as generalized, and adrenal obesity as involving the face, neck and body, but less marked in the extremities.

To diagnose the condition of the adrenals, air injection of the perirenal fascial spaces, followed by its visualization by x-ray, has been used by us in all the established cases, and also in others where an adrenal lesion was suspected. This method,[20] more than any other except exploration and direct vision, has at least given us some intimation as to whether gross anatomic changes are present. A tumor was diagnosed in 9 of our cases by the use of air injection and x-ray. Bilateral adrenal hypertrophy was diagnosed in 2 others. Gross changes which could be considered as tumors were not seen in any of the other cases. In a number of cases reinjection and x-ray photography were carried out and the shadows were compared with the earlier ones, in order to see whether any change had taken place. In 6 cases the adrenal could be visualized only on one side. When the proper fascial plane was not injected in such a way as to visualize the adrenal, this side was usually reinjected with larger amounts of air. This usually resulted in the visualization of the correct fascial planes.

The early studies on excretion of sex hormones gave a rather puzzling picture.[21] In tumor cases, women with amenorrhea and a masculinizing syndrome showed what was considered to be normal amounts of urinary female sex hormone. Why such patients, with apparently normal amounts of hormonal excretion, did not menstruate was not clear until Gallagher[22] showed that they excreted large quantities of male sex hormone, in fact larger amounts than were found in the urine of normal adult males. A reduction of the excretion after removal of the tumor was also shown. Encouraged by the possibility that such a hormonal test might be an important factor in the diagnosis, Kurzrok[23] made further studies on tumor and non-tumor cases which showed that excess amounts of male sex hormone were excreted in cases of adrenogenital syndrome without tumors' being discovered either by air injection and x-ray or by operation and section. One of the largest amounts was found in a non-tumor case with hirsutism, dysmenorrhea and obesity.

It seems, so far, that excessive amounts of male sex hormone in the urine are associated with androtropic tumors. It is reduced on their removal, but the hormone may be present when no tumor can be shown, and in amounts that vary with the masculinization of the patient. With the removal of half of an adrenal in some non-tumor cases, the adrenal that was sectioned had some association with the hormonal excretion because of clinical improvement, as first shown by Broster and Vines.[19] We were able to confirm this. Diminution of the amount of adrenal cortex appears to be followed by a concomitant decrease in hormone excretion.

Recent investigations by Reichstein,[24] by Wintersteiner and Pfiffner[25] and by Kendall et al.[26] have shown the presence of a number of sterol-like substances (steroids) in the adrenal cortex. Some of these are easily converted into substances with male hormone activity (androgenic), one androgenic steroid occurring naturally in the adrenal. From the urines of cases of adrenal tumor and of adrenogenital syndrome, a number of steroids were isolated by Callow,[27] by Burrows, Cook, Roe and Warren,[28] by Broster and Vines[29] and by Butler and Marrian.[30] Some have been identified chemically and have revealed androgenic properties; others have not yet been identified chemically nor tested physiologically. Of particular importance, however, is the compound pregnane-3, 17, 20-triol, recently isolated by Butler and Marrian[30] from the urine of women with adrenogenital syndromes. The excretion of this steroid seems to be associated with the syndrome, since it does not take place in

men or in normal pregnant or nonpregnant women, and since the steroid was not found in the urine of a case of adrenal tumor after removal of the enlarged gland. Report upon its physiological properties will be awaited with interest, as will comparison of such findings with those in other adrenocortical tumors.

PATHOLOGY

Most of the tumors are reddish-yellow and globular or ovoid, and have a thin, fibrous capsule. There may be invasion of the neighboring organs, the kidney being involved most frequently. The histology varies, although certain types often show a constant symptomatology.

In the male without endocrine symptoms, it was not possible even to guess from which cell structure of the adrenal cortex the tumor was derived. Section showed many large irregular cells with very large and bizarre-shaped hyperchromatic nuclei, often with mitotic figures and a pale, granular cytoplasm. These tumor cells showed a deep fuchsinophilic reaction in the cytoplasm with the trichrome stain, similar to the cytoplasm in the cells in adrenals from adrenogenital syndromes as described by Broster and Vines,[19] which they suggested were characteristic of that syndrome. We have examined sections of an adrenocortical tumor sent to us by Dr. N. W. Roome of the Department of Surgery, University of Chicago. This tumor was removed from a man who had no endocrine symptoms. The sections resembled that of our male case, with perhaps fewer giant cells to the field. The main cellular structures of these two tumors resembled each other, however.

In the female without endocrine symptoms the tumor resembled more the zona fasciculata of the adrenal, although other sections in places resembled the other two layers. As a whole this tumor more closely approached those described as renal hypernephroma than did any of our adrenal tumors. Sections stained to determine fuchsinophilic granules showed that the cells contained them in only small amounts.

The tumors from cases with virilism varied from obvious carcinomas to what have best been described as adenomas. The cells of the malignant tumors were of relatively uniform appearance, although they varied in size. They were rather large and irregularly rounded or cylindroid, with well-defined cell membranes and a voluminous, faintly acidophilic cytoplasm. In some areas the cytoplasm was vacuolated, as if containing lipoid. One of the carcinomas — from a case with marked sex changes — had a considerable proportion of cells that stained with fuchsin and showed a bright-red cytoplasm. In the others the proportion was less marked. As a whole it appeared from careful study of these sections that the tumor cells resembled more the inner or reticulate layer of the adrenal than they did either of the other layers. Grollman[31] suggests that such a layer may be concerned with certain phases of reproductive symptomatology, and may contain cell inclusions from the gonad which assume gonadal function in tumor growth. We have seen no evidence in our microscopic studies to support this suggestion. Broster and Vines[19] described specific staining reactions of the cells of the adrenal cortex in cases of masculinizing syndromes and tumors. These we also encountered, but we have been unable to show the uniform predominate amount of such cellular staining as described by them. Further studies will be of interest.

The adenomas showed a large proportion of cells to have a cytoplasm filled with vacuoles, presumably lipoids, and clusters here and there of cells from the three layers of the cortex. It was impossible to derive from most of the vacuolated cells any suggestion as to their origin. The cells contained more or less the same amount of fuchsinophilic granules as was seen in controls.

Portions of the adrenals removed in cases of adrenogenital syndromes without tumors showed in most a cellular structure little changed from normal. Special staining in some cases showed an increase in cells with fuchsinophilic granules, but not to a predominant extent. It is possible that the portions of the adrenals removed by us may not have contained such areas, as described by Broster and Vines. We endeavored to remove a half or a third of a gland — first from what was demonstrated by air injection and x-ray to be the larger adrenal, and next from the thicker portion of that adrenal.

In one tumor sufficiently large for assay, Pfiffner[32] reported that life-maintaining hormone was not present in sufficient quantities for demonstration. Nor could Kurzrok[23] demonstrate any female sex hormone in this tumor. Although a steroid with androgenic activity has been isolated from the normal adrenal cortex, none has as yet been demonstrated in an adrenal tumor.

TREATMENT

Surgical exploration is indicated in tumor cases. Transperitoneal incision permits exploration of the entire abdomen, together with examination of the ovaries and the spermatic fascial planes where adrenal rests may occur. It also allows ligation of the vascular supply of the tumor before its manipulation, and theoretically lessens dissemination.

In the cases of tumors without endocrine symptoms the growths were so silent that they had

reached a large size before discovery. In the cases showing no demonstrable metastases the tumors were removed with only such technical difficulty as was caused by their size. Two of these patients made uneventful postoperative recoveries.

In the tumors with endocrine changes the operative risk appears to be better in cases with well-marked androtropic symptoms and with little metabolic change. This is especially true if a normal adrenal shadow is visualized on the opposite side and the presence of the second gland is confirmed at exploration. One such patient made an uneventful recovery. The patients with marked changes in metabolism are poorer risks. Three of our tumor patients went into acute adrenal collapse shortly after removal of the tumors. Two had well-marked metabolic changes with apparently normal-sized adrenal glands on the opposite side, while the third showed only a tiny shadow. One patient recovered with the help of multiple blood transfusions and saline infusions. Since she died later of metastases, there were evidently secreting tumor cells in these which may have influenced her recovery from the adrenal collapse. In the remaining 2 cases one patient died twenty-seven and the other thirty-two hours after removal of the tumor. Administration of a commercial preparation of life-maintaining hormone did not change the rapid fatal collapse in either case. Only slight and fleeting improvement followed blood transfusions and saline infusions. These cases showed a marked elevation of temperature, a very rapid pulse and a fall of the systolic blood-pressure readings to 50 or thereabouts. The patients were rational, observant and apparently comfortable up to a terminal convulsion. In both cases the tumors were small, one being a carcinoma and the other an adenoma. In the carcinoma the opposite adrenal was tiny. In the adenoma, a normal-sized opposite adrenal was visualized, but on autopsy it was shown to be thin and with atrophic cells. It has been suggested that in tumors of this kind, which are secreting large amounts of hormone necessary for plasma tone and function, the flooding of the organism by the tumor cells with such hormone or hormones causes functional and actual atrophy of the opposite adrenal. Support for this explanation has been advanced experimentally, especially by Ingle and Kendall,[33] who showed that the administration of large amounts of cortin to a normal rat over a sufficient period of time produced atrophy of the adrenal cortex. In addition, they have demonstrated that such an atrophy can be prevented by the administration of a fraction of anterior pituitary extract which has high adrenotropic activity. Such experimental evidence explains why collapse is less frequent in patients with changes of the sex type, and suggests in cases with metabolic changes a preliminary course of injections of fractions of such a pituitary extract, before operative removal of the tumor. Whether such injections will produce reactivity of functionless adrenal cells awaits demonstration.

Parts of the adrenals were removed in selected cases of adrenogenital syndrome without demonstrable tumors. In 2 of these cases, on account of obesity, operation was effected through the flank; the others were all explored by an anterior transperitoneal exposure, which allowed a thorough examination of all possible areas of adrenal rests as well as examination of the ovaries. The incision was made on the side of the largest adrenal and a section was removed through its densest portion. The deep location of the adrenal and its blood-vessel attachments makes such a procedure somewhat difficult in the obese, despite all types of mechanical aids. There was no postoperative mortality or complications in these cases.

RESULTS

Adrenal tumors without hormonal symptoms showed large, silent carcinomas that had been growing for a considerable period. Such tumors do not offer a high percentage of cures. Of our 3 cases of this type, 1 died without operative interference, 1 died of pulmonary and liver metastases one year after removal of the tumor, and 1 is alive, apparently without metastases, more than a year after operation.

Adrenal tumors with androtropic changes, if operated upon early enough, have a fair prognosis. They are usually of slow growth and remain encapsulated for some time. It has been our hope that air injections of the adrenals will demonstrate these tumors earlier than they are usually diagnosed. A number of operated cases have been reported as having had several years of follow-up without a recurrence. One we have followed for over three years without demonstrable metastases. Where metastases have occurred they have shown themselves by a recurrence of the syndrome. They have appeared most frequently in the lungs. There is usually a quick symptomatic recovery in these cases, especially in the menses and in the secondary sex organs -- breast, clitoris, and so forth. The younger the subject, the more rapid is the recovery. That in the hirsutes varies; it is usually satisfactory except on the face, especially in those that have shaved. No improvement occurs in such fixed changes as dentition and closure of the epiphyses.

In the cases of adrenogenital syndrome without tumor, the administration of female sex hormone over varying times has in most cases given no lasting results. Following the bilateral injec-

tion of air around the adrenals in several cases of amenorrhea, we have, strangely, seen the return of menstruation but have found no explanation of the phenomenon. In cases submitted to exploration there has been some improvement in the symptoms after the exposure and removal of portions of the adrenal cortex, mostly in the menstrual sphere. Changes varied from a return of the menses to an increased regularity or an increased flow. In several cases there has been improvement of the body contour with a change in breasts and hips. There have been disappointingly few and slight changes in the hirsutism, with usually no change on the face. This has been one of the factors that has kept these women psychologically upset. We have seen no changes in the genitalia or in the voice.

One of the cases of tumor showed upon later air injection and x-ray an increase in the size of the remaining adrenal. A somewhat similar increase of the untouched adrenal apparently occurred following operative removal of a portion of the other adrenal in cases of the syndrome without tumor. A continuation of the study of these cases will show whether such a change will be accompanied by a recurrent increase in the symptoms of the syndrome.

SUMMARY

Adrenocortical tumors may occur without evident endocrine changes, but they are usually accompanied by characteristic hormonal changes. These are of three types: (1) changes in the secondary sexual characteristics toward masculinity in the female (androtropic) and rarely in the male toward the female (gynecotropic); (2) maturity in the young and more advanced age in the mature; (3) changes in the metabolism of plasma, fat and skin. In some cases one or the other type may predominate.

Similar endocrine changes called the adrenogenital syndrome, occur without any demonstrable tumor, but the symptoms are usually longer in duration, less pronounced and more variable, and not infrequently have a familial tendency and resemble the experimental intersexual animal or freemartin.

The adrenals may be visualized by x-ray after perirenal air injections.

The urinary sex hormones are usually excreted in amounts varying with the sexual changes, and seem to occur in both tumor and non-tumor cases. The excretion of male sex hormone is reduced following removal of a tumor, and apparently is also reduced following diminution of the adrenal cortex by operation when no tumor can be discovered. A specific hormone may be excreted with some tumors.

The cellular structure of the tumors varies. The androtropic tumors most nearly resemble the reticulate layer. Fuchsin granules in the cytoplasm of cells have been demonstrated in both hormonal and non-hormonal tumors, but appear to be more predominant in the former.

The removal risk in cases of androtropic tumor is less than in those in which marked changes in metabolism occur, because in the latter, atrophy of the opposite adrenal is frequent. This atrophy has a suggested preoperative therapy.

Removal of the tumor produces a symptomatic cure but does not correct the fixed anatomic changes. The facial hirsutism often persists. When removal of a tumor is followed by metastases, the same endocrine changes recur that were present with the original tumor.

With operative decrease in the amount of adrenal cortex in non-tumor cases, there are some symptomatic changes. These are most marked in the menstrual sphere, with some changes in the body contour and psychologic state, and with little or no changes in the hirsutism, and in the genitalia or voice.

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Discussion

Dr. Charles H. Lawrence: I agree that these tumor cases show several different types, and that we do not know as yet what kind of tumor goes with each type of symptomatology. I thought perhaps it would be interesting to report 3 cases in which the results are fairly well established, and tend perhaps to emphasize several of the things that Dr. Cahill mentioned.

Case 1. A girl of 13 years and 10 months was first seen in 1928. There was nothing of significance in the family history, except that the mother and one sister had had irregular and profuse periods. The patient had had an operation for acute appendicitis. She began to menstruate at 10 years and 8 months, which suggests that possibly some endocrine disturbance was already producing early maturity. During the next 9 months her periods occurred every 28 days, without pain. In June, 1928, she menstruated normally, but had not done so since that time. During the first 6 months that we followed her she had anemia, but there was no change in her general condition.

One of the striking things is the relation between the development of symptoms and the time when it becomes possible to make an accurate diagnosis of adrenocortical tumor. Little attention was paid to her lack of menstruation until June, 1927, when masculine tendencies were first noticed — there was hair on the face and chest, and the voice became deeper. Her general health was excellent.

Physical examination showed a normal, well-developed female. There was acne on her face and back, which is a common symptom of adrenocortical tumor. There was dark, coarse hair on her arms, legs and back, and her pubic hair extended up to her navel. Her clitoris was larger than normal. Rectal examination revealed a rather small uterus. There was no other pelvic abnormality. Nothing was shown by abdominal examination. The physical findings were otherwise normal. The laboratory examinations were all negative. The basal metabolic rate was normal. A kidney function test was normal. X-rays of the skull, kidney and urinary tract showed no lesions. The eye grounds and visual fields were normal. Pelvic examination under an anesthetic showed no abnormality except a small, hypoplastic uterus.

We thought of a tumor of the adrenal cortex, a tumor of the ovary and possibly a tumor (basophilic) of the pituitary gland or one of the pineal gland, but there was nothing upon which we could establish a diagnosis. The patient was kept under observation for a year, and her condition remained essentially the same. At the end of that time she was seen by the late Dr. D. L. Jackson, who thought there was sclerosis of the ovarian cortices. Exploration revealed a small uterus with no endometrium. The ovaries were also small. There was retroversion of the uterus; the tubes were normal; the ovaries were smooth, with thickened cortices, and were packed with small cysts which were evacuated. The left kidney was normal on palpation; no abnormality of the right kidney was found, although the operator was not sure he had felt the adrenal. There was an uneventful recovery and no change in the symptoms. The patient was seen at 6-month intervals for the next 6 years, with no significant development until September, 1934, 5 years after operation. At that time she had developed moderate dyspnea and palpitation on vigorous exertion. This was the first new sign after the original development of masculinization. The systolic blood pressure, which had been normal, rose to 180. The retinal arteries were not found to be narrowed. Hair appeared around the areolas.

An abdominal examination was negative. Pyelograms showed the right kidney to be larger than the left. The infundibuli and calices filled well. Neither Dr. G. C. Prather, who saw the x-rays, nor Dr. L. R. Morrison felt that there was enough evidence of tumor to justify an operation. In April, 1935, x-rays were again taken. The slight hypertension persisted. On palpation a definite mass was felt in the left flank. Pyelograms showed numerous areas of calcification in the region of the tenth lumbar vertebra and the tenth rib. There was a suggestive mass overlying the left kidney. The patient was operated on, and a tumor of the left adrenal was removed. It was completely encapsulated, and scattered throughout were small spicules of bone. Because of the size of the tumor it was necessary to remove both the adrenal gland and the kidney. Soon after the operation there was a fall in blood pressure. Many generous doses of Eschatin were given. The blood pressure stopped falling, and the level of the blood-pressure readings seemed to depend upon the size of the doses of Eschatin. There is some difference of opinion as to the physiologic action of products of the adrenal gland now on the market, but Eschatin did seem in this case to have some effect in raising the blood pressure.

Before the patient left the hospital the timbre of her voice returned markedly to the feminine, and in 2 months it was back at normal. She began to menstruate in September. From that time she has continued to menstruate perfectly normally. This is interesting in the light of her ovarian lesion and the operative trauma to the ovary.

One year after operation examination showed some little gain in weight, which had been normal. Although there was a marked degree of hypertrichosis, this was not bothersome because the patient shaved daily. A year later it had practically disappeared. Only a little hair was left on the face.

It seems interesting that the tumor must have been there for at least 5 or 6 years before definite symptoms allowing diagnosis could be made, although clinically the diagnosis was determined before operation.

Case 2. A 24-year-old woman was first seen in March, 1934, in coma. The family history was negative and the past history not remarkable, except that she did not menstruate until she was nearly 16. Catamenia were regular

and normal for 2 years. She then developed menorrhagia with moderate secondary anemia, which persisted until the age of 21. At that time she had a flat sugar-tolerance curve. Physical examination showed nothing remarkable except that the uterus, according to Dr. F. S. Newell, was small. After 3 months of treatment with Antuitrin S the menorrhagia disappeared; it did not recur. From then until early in 1936 the patient appeared to be in perfectly normal health. Her current illness began while driving a car, when there was blurring of vision, and faintness. She was able to drive home, and after luncheon felt normal. The next night after retiring she went to her sister's room and returned to her own room. She was heard to fall; and when found, she articulated with difficulty and her speech was incoherent. After drinking a glass of orange juice she seemed as normal as ever, but did not remember going into her sister's room. For a week following the bout of fainting, she was well, and then fell into a coma, from which she could not be aroused.

Physical examination showed a normally developed individual. The blood pressure was normal. The pupils reacted to light. The reflexes and heart and lungs were normal. A mass was palpated which extended from the left caudal region to the left flank, and was resilient. The blood sugar was 40 mg. per cent. The plasma carbon-dioxide-combining power was 51 mg. per cent, and the urine acetone 4+. The administration of 1000 cc. of 10 per cent glucose was started. The patient regained consciousness after 50 cc. had been given, and was able to answer questions before the dosage was completed. She had been aware of a prominence in the left upper quadrant for 2 or 3 months, but thought it was only a roll of fat. She was seen by Dr. E. L. Young, who suspected a pancreatic cyst because of hypoglycemia and low blood pressure. Exploration revealed a large, bluish-red mass, which was highly vascular. It extended backward into the posterior abdominal wall, and appeared to be fixed. A trocar was introduced, but no fluid was obtained. Removal was impossible and a small specimen was excised and the wound closed.

Examination showed the growth to be a cancer growing with moderate speed and originating in an endocrine gland. Whether it arose from the cells of Langerhans or the adrenal cortex was not known, but the latter was considered to be more probable. There was a slow and uneventful recovery from the operation.

The blood sugar varied from 41 mg. per cent to lower levels. There was a later reading of 61 mg., and the last one taken was 60 mg. The low readings were not always accompanied by clinical symptoms of hypoglycemia. The blood picture was normal. Determinations for urinary prolan and estrin were negative. Menstruation continued for 2 months and then ceased, and has not been re-established. X-ray treatment was given; during it there were no major hypoglycemic attacks, although the patient occasionally felt dizzy.

On July 10, 1936, the x-ray treatment was discontinued. In October coma frequently recurred, but it invariably responded to intravenous glucose; the blood-sugar content at that time was 110 mg. per cent. Acne, which was present at operation, grew steadily worse; it involved the entire face, chest and back, and there was also marked acanthosis of the axillae. The tongue became thick, and so did the subcutaneous tissues of the shoulder and neck. This condition did not resemble simple obesity. The blood chemistry was entirely normal. Hormone assays were again done, but no signs of prolan or estrin were found. Other x-rays were taken but no metastases were found. On October 13, 1936, a second attempt was made to remove the tumor, by Dr. W. E. Ladd, who used a flank incision, but this was found to be impossible. Diagnosis of a tumor of the suprarenal cortex was confirmed.

There then occurred a number of interesting developments. For 36 hours after the operation the temperature rose to 104.4°F., and the pulse from 120 to 180. The blood pressure fell to 120/50. The patient became unconscious but was revived after intravenous glucose. The blood picture and the physical examination were both normal. On the 3rd day after operation there was marked improvement; the temperature was 101°F. and the blood pressure returned to normal. During the next 2 weeks there was marked general improvement. The subcutaneous thickening had almost disappeared. The acne and the acanthosis also practically disappeared. The patient left the hospital in good condition, and no more hypoglycemic attacks occurred.

A month later the patient's condition grew worse. Her systolic blood pressure rose to 190, and she developed edema of the lower legs. Dullness in the lower abdomen was occasionally demonstrable. Attacks of coma became more and more frequent. During one of them delay in preparing glucose forced us to give 1 cc. of adrenalin. The effect was surprising, and before the glucose could be brought into action the patient recovered. Since that time we have repeated the adrenalin, and find that as little as 0.3 cc. of a 1:1000 solution restores the patient to consciousness just as efficiently as does glucose.

This is an interesting endocrine situation, one which we can only explain by saying that the hypoglycemia is not due to exhaustion of sugar reserve, but to a break in the chain which renders it impossible for her to take glycogen from the liver when the blood-sugar content gets too low. Adrenalin seems to fuse the chain again, and the blood sugar becomes normal.

The patient showed very little loss of strength. In January, 1936, she had another exacerbation. After consultation with Dr. E. D. Barringer and Dr. James Ewing she was sent to New York and given radium packs; since then she has had x-ray treatment. On April 9, 1936, I examined her because of failing vision. At that time examination of the eye grounds showed only moderate sclerosis of the arteries but no exudate or hemorrhages. Since then, I have heard, her vision has improved. The lesion is probably circulatory. I have not seen reported in the literature any disturbance of carbohydrate metabolism like that which this patient shows.

Case 3. In this case the clinical picture was difficult to distinguish from that of pituitary basophilism. The patient, a 30-year-old white woman, entered the hospital in 1934 because of blurring of vision of 18 months' duration. There was a history of polyuria and nocturia of 9 months' duration, and of undue fatigue for several years. The patient had always bruised easily. There was an increased growth of hair the previous year, the new hair being red and fine (she was red-headed). One of her brothers had died of diabetes. Otherwise the family history was normal, as was her past history. Her periods started at 11—a bit early. They were regular until 1931, when they were irregular for a month and then stopped; the patient's voice became harsh and her hair coarse, and she gained 25 lb. in weight. At that time she was seen at the Lahey Clinic and was found to be overweight and nervous. Her heart was moderately enlarged and the aortic second sound was accentuated. The blood pressure was 240/130. The pelvis was negative. There was edema of the lower extremities. The eye grounds showed no abnormality. The nonprotein nitrogen was 32 mg. per cent. The blood picture was essentially normal. The specific gravity of the urine varied from

1.005 to 1.014. A diagnosis of primary hypertension was made.

During the next few years there was increased fatigability, and for the last year before admission it was necessary for the patient to remain in bed a day or two at a time. Blurring of vision increased steadily, and there were fixed spots before the eyes for 2 weeks before admission. Reading was difficult. The eyelids became puffy, and it required effort to hold the eyes open. On admission, there was an increase of the hair on the face. The skin was black and blue over the lower legs and ankles, and the feet were swollen. There was reddening of the facial skin. Obesity was localized in the abdomen and breasts. There was pitting edema of the legs. Reddish-blue striae occurred on the medial aspect of the thighs. There was an increase in hair. The fundi showed characteristic choking of the disks, with exudation in the right eye. The lips were cyanotic, and the skin was dry and scaly.

There was much discussion in the hospital as to whether there was a basophilic or an adrenocortical tumor. The neurological examination was negative. The patient showed a tendency to increased production of red blood cells, and had a hemoglobin of 103 with 5,500,000 red cells. The blood cholesterol was also high. The nonprotein nitrogen was 52 mg. per cent. The glucose, following a tolerance test, showed a high curve, registering 246 mg. in half an hour. The curve remained high (172 mg.) at the end of the test. The urine showed normal dilution and concentration, with a phenolsulfonphthalein of 49 per cent. The albumin was constant, between 1.0 and 1.5 per cent on numerous examinations. The sediment showed many finely granular casts. A pyelogram was negative, and x-ray photographs of the skull showed no evidence of tumor. The electrocardiogram was normal. The blood pressure was 200/160. The basal metabolic rate was normal. The general consensus, myself dissenting, favored a diagnosis of malignant nephrosclerosis with pituitary basophilism. I insisted on a diagnosis of adrenocortical tumor until Dr. F. H. Lahey operated and removed a left adrenal tumor. The blood pressure fell to 120 and continued to fall in spite of intravenous injections, including Eschatin, and the patient died. Postmortem examination showed absence of the left adrenal gland and extreme atrophy of the right one, which weighed less than 0.5 gm. The capsule was thickened and the medulla almost absent. A few cortical cells remained. The right gland contained cysts as well. Microscopic examination revealed an adenocarcinoma. Serial sections were made of the pituitary, but careful search failed to show any signs of basophilism.

These three cases bring out some interesting considerations regarding the endocrine glands. In the first case, masculinization was marked; in the second, there was little masculinization but an odd change in carbohydrate metabolism; in the third, there was masculinization, but of a moderate type. All three patients had adrenocortical tumors. The very early onset of menstruation in the first case and the definitely late onset in the second suggest that the excess of hormone may have been due to a pituitary factor long before the clinical picture had developed.

A Physician: What was the pathological report in the first case?

Dr. George C. Prather: Carcinoma simplex.

Dr. Fuller Albright: I should like to ask one question. We are indebted to the Presbyterian Hospital in New York City not only for knowledge concerning increased and decreased function of the adrenal gland, but also for the fact that Loeb first called attention to the fall in sodium in Addison's disease. Have you carried out studies in order to see whether any abnormality in sodium accompanies excess adrenal function?

Grollman's belief that the androgenetic hormone is produced by another cell in the adrenals is entirely theoretical, in that the hormone is assumed to come from some remnant which yields masculinizing hormone. If this were the case, we should not find atrophy of the other gland. To do so would be strong evidence against Grollman's theory.

I was very much interested in the mention of polycythemia and decreased blood volume. We have found these at the Massachusetts General Hospital; they may constitute a very important clinical point. Many patients die in a state of shock after an operation on the adrenals. This has been explained by the fact that the other gland has atrophied. It is probable, however, that some of these patients succumb to shock due to the decreased blood volume.

I was hoping to hear something about bones, for we are very much interested in this subject. The osteoporosis which occurs in some of these cases is significant. In 1 case the presenting symptom was a decrease in height. The patient eventually died from an adenocarcinoma and stones in the kidneys. There is an increased excretion of calcium in the urine in spite of the normal blood calcium and phosphorus. This patient showed a perfectly normal parathyroid post mortem, so that the increase in decalcification cannot have come from that. We think that bone disease is due to senile osteoporosis; after all, it consists very largely of increased precocity. There is heightened sex development, and also mental and physical development. The same thing happens if there is an increase in secretion by the adrenals; thus, precocity in the adult results in senility, which, in turn, causes changes in the bones.

Dr. Joe V. Meigs: I should like to ask about the second slide in the case of adrenocortical tumor; may this not have been a chorioepithelioma, and was not the man demasculinized? It looked to me like a chorioepithelioma, and if it were, such a diagnosis would be very interesting. Secondly, in masculinizing tumors in the female the hormone is produced separately by the lining cells, which are present and can be seen in the arrhenoblastoma. They stain with soudan iii. It may be that the clear cells were the cells of this tumor, and that the masculinizing hormone recovered in the urine was produced by them.

Dr. George W. Holmes: The roentgenological problem is to establish the presence or absence of these tumors. In order to do that one must have the best quality of films. Whether we can improve the technic by newer methods is somewhat problematic, but it is expected that we may do so with fast machines and better focus points. It may be possible for us to help more than we do at present. We depend upon the air injection, which must be properly done; otherwise the x-ray is of no value.

The next problem is the interpretation of the film after we have developed it. The adrenal gland is of many shapes and sizes, and when we look at x-ray pictures of it we see only the projection of the shadow in one of many planes. It is very difficult for us to describe the gland. Dr. Cahill has been able to diagnose accurately some of the larger and more characteristic tumors. I fear we shall always have trouble with the smaller and less characteristic ones. I have not had an opportunity myself to carry on this work, but I have seen others do so. Dr. Richard

Schatzki is here and can probably give a better interpretation than I can.

Dr. Richard Schatzki: I should like to ask two questions. Has Dr. Cahill any standards as regards the size of a normal adrenal x-ray picture? We have had decided difficulty with borderline cases, and described one medullary tumor as an upper limit of normal, whereas it was abnormal. Has he used lateral films in order to demonstrate the thickness of adrenal tumors? We have tried them unsuccessfully.

Dr. William C. Quinby: I want first to compliment Dr. Cahill on his adept handling of a very abstruse subject. He has not described a single type of case tonight. He has described cases of the adrenogenital complex in which there apparently was no lesion in the pituitary; and in some cases I do not feel that he has succeeded in demonstrating adrenal lesions either. This is a very complicated subject, and one on which we have been privileged, tonight, to hear the most advanced opinion.

To take up the subject serially, the injection of air around the kidney in order to demonstrate either renal or adrenal tumor I tried out a number of years ago. It is not an accurate method of examining either type of tumor, especially the adrenal. Everything depends upon the situation in the given case. In the first place, the injection must be made into the renal fossa. There are no results if it is made in the substance of the psoas muscle. The amount of air injected must be in excess of that which one would ordinarily inject for the demonstration of renal tumors. Furthermore, air is much better than oxygen, and nitrogen is better than air, the point being that one should inject a gas which is slowly absorbed, and make x-ray observations at stated intervals afterward. One usually gets a very confusing picture of either renal or adrenal tumor within five or six hours after injection of atmospheric air around the kidney or into the renal fossa. The injection in every case, so far as the procedure goes, is similar. It makes no difference whether you are trying to outline the adrenal or the kidney.

The interpretation of x-ray films is still somewhat questionable. The roentgenologist is doing his best to help us, but we must make many more injections before standardization becomes possible. The opinion in any one case may be either for or against the possibility of a tumor. A good many cases in which the adrenal is definitely at fault, as has been shown by Dr. Cahill, do not show a definite enlargement of the adrenal in the x-ray films. Similarly, conditions in the pancreas or the parathyroids can well cause overfunction, which produces the symptoms of disease, without very much in the way of a demonstrable tumor. It is absolutely impossible in cases of hypoglycemia that have been successfully operated on, and that have been demonstrated by surgeons. An analogous situation probably exists in regard to the cortex of the adrenal gland. I am in doubt as regards tumors of the medulla, which are quite different in their clinical manifestations. What we are discussing, as I understand it, is tumors of the cortex of the adrenal. Undoubtedly a good many start or remain as adenomas, and only later do they become definitely invasive neoplasms. To be able to demonstrate such a condition in the adrenal in the early stage is beyond the reach of any roentgenological procedure that I know about. We must therefore depend largely on clinical manifestations. The reports of increasing numbers of patients — and, as Dr. Cahill tells me, they are large — will eventually bring a certain amount of clarity to a state of mind which in my opinion is still chaotic.

In the first place, we must eliminate tumors of the pituitary, because we know that this gland is probably primarily at fault in a good many variegated conditions affecting the secondary sex sphere. These have largely been excluded by x-ray of the sella turcica. We next come to the question of what sort of adrenal the patient has. Within our present limitations we must be willing to investigate the adrenal by open operation. There are definite instances in which the clinical picture is characteristic; in spite of the fact that we may not be able to demonstrate any very striking differences from the normal through such procedures as the injection of air.

I call to your attention also the fact that, speaking clinically, most tumors of the adrenal cortex, so far as we know them today, have as their clinical effect an increase in masculinization. In women the changes lie in the direction of virilism. In men they lie in the direction of precocious puberty or hypervirilism. In many such cases the condition can be made clear by the pediatrician. My experience has been with individuals in whom the diagnosis should have been made while they were under the care of the pediatrician, not that of the urologist.

Two or three years ago I reported a case in which a child had been born and bred under the best possible circumstances and had been known to be precocious from his second year of life. He had gone through school at an early age, and was prematurely developed in body as well as in mind. He received no medical attention until, at the age of ten, while running a race, he had an acute abdominal crisis. Investigation revealed an abdomen full of blood, and it was later found that the free hemorrhage had been caused by rupture of an adrenal tumor as large as the patient's head. There were present hypertrichosis, acne, a decreased amount of sugar in the blood, hypertension, and every other condition needed for a diagnosis of adrenal tumor; but in that day it was not appreciated that the child probably had an adrenal tumor which eventually became malignant, and which might have been removed before it had become invasive, his life thus being saved. There was a perfectly normal adrenal on the other side. In many other instances, of course, the other adrenal is atrophied.

Dr. Cahill (closing): I am in accord with Dr. Quinby's statements in their entirety. I have taken special care to limit my statements to known facts. I gave no hypotheses and no theories, and I said that we used only the tools available at present in trying to arrive at a diagnosis. In 27 of the cases we diagnosed tumors in only 6, although the others had symptoms. I operated on many of them, following Dr. Quinby's idea exactly.

In making x-ray pictures we take them serially, injecting air one day and taking them the next; we then repeat the procedure, looking for a lead, and that is all we do. The technic is imperfect, but at present it is the only means we have of detecting adrenal tumors.

In answer to one question, collapse occurs in some cases from hemorrhage into the abdominal cavity; in other cases I believe that collapse and death are the results of handling of the adrenal gland. In about 15 per cent of the entire population only one adrenal gland is functioning normally.

There are many functions of the adrenal gland, and many hormones. As shown by some of the reported cases, there are hormones producing masculinization and maturity; the latter is a tremendous force in the body, closing off the epiphyses and producing old age rapidly. There is the famous case in France of a patient who advanced from childhood to adulthood, became a father, and died of old age within ten years.

Dr. Loeb studied all our cases with us. We could not demonstrate any abnormality in the sodium balance, and apparently there was none. In the adrenal cortex there must be cells with many different functions, and the final result depends upon the interrelation of the whole. We are just trying to make hypotheses in the direction in which it goes. We have tried to determine the particular change in salts which produces collapse. This factor is apparently known in animals, but whether it exists in human beings we are not aware. A woodchuck whose kidneys and adrenals are removed can live for four to six weeks in the winter, but only two days in the summer. What has hibernation to do with such things? The question is a fascinating one. I did not indulge in those phenomena but only tried to call attention to the observations which seemed unassailable to ourselves.

In the second slide, it is true, the cells resemble those of a chorioepithelioma. In our experience these produce gynecomastia and large amounts of prolan A. In fact, one can make the diagnosis of testicular tumors according to the amounts of prolan.

What constitutes a normal x-ray picture I do not know as yet. I have made over one hundred so as to see what improvement can be made in present methods, and to gather experience and determine whether the glands are normal or abnormal. I admit that we may never get anywhere, but we are only using these tools to see how far we can go. We have not had very much success with lateral films.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 24191

PRESENTATION OF CASE

First admission: A sixty-two-year-old Russian Jewish woman entered the hospital with the complaint of fluid in the right chest of three years' duration.

Seventeen years before entry the patient began to have a persistent nonproductive, brassy cough and felt that there was "something in her chest that should be coughed up." She had no hematemesis, hemoptysis, dyspnea, orthopnea or peripheral edema. She was treated by her physician for six months without appreciable benefit and at the end of that time entered an outside hospital where by x-ray a large substernal mass was found. Bronchoscopy showed evidence of marked pressure on the trachea at its bifurcation. A biopsy of an axillary gland showed no evidence of metastasis. She refused operation and went to another hospital where she was given a course of radiation lasting over a period of many months. This gave her prompt relief, and she had no symptoms until three years before entry, when she had pneumonia which lasted about a month. She lost about 25 or 30 lb. in weight and did not seem to recover completely from the illness. She had difficulty in breathing and orthopnea, and her physician found a right-sided pleural effusion, which he tapped. From that time until the time of entry she had repeated reaccumulations of fluid, which were tapped on nineteen occasions. As the fluid accumulated she had dyspnea, orthopnea, some distention and tenderness in the region of the liver and spleen, but no peripheral edema. Her appetite was rather poor, but her stools were normal, and there was no tendency to constipation. She had no other significant symptoms except weakness and a total weight loss of 40 lb. during her entire illness. One year before entry she was given another course of radiation by deep x-ray, which was carried out over a period of nine months. The treatment had no apparent effect and did not decrease the size of the mass. The fluid withdrawn at the various taps was yellowish in color and on one occasion bloody; search for tumor cells in it was negative. Guinea-pig tests were negative. Her past and family histories were entirely negative.

Physical examination revealed a fairly well-developed but poorly nourished woman in no great discomfort. There was marked dilatation of the superficial veins on the upper arms and anterior aspect of the chest. In the lower anterior part of the neck a smooth, symmetrical, moderately firm mass was palpable extending down into the neck. There was dullness over the lower two thirds of the right chest, with practically absent breath sounds at the right base. A few moist rales could be heard at the left base. The heart was slightly displaced to the left, and there was a harsh apical systolic murmur. The blood pressure in the right arm was 195 systolic, 80 diastolic, in the left arm 190 systolic, 80 diastolic. The liver edge was palpable two fingerbreadths below the costal margin. There was no edema of the extremities.

The temperature was 98°F., the pulse 80. The respirations were 22.

The urine examination was negative. The blood showed a red-cell count of 5,090,000 with 80 per cent hemoglobin, and a white-cell count of 7700 with 75 per cent polymorphonuclears. The Hinton test was negative. An attempt to determine the basal metabolic rate was unsuccessful because of lack of co-operation by the patient. An electrocardiogram showed slight tendency to left-axis deviation and T waves which indicated a possible digitalis effect.

X-rays of the chest showed a large fairly symmetrical mass occupying the upper mediastinum and displacing the esophagus to the left and the trachea to the right. The trachea was considerably narrowed in the region of the thyroid, but neither it nor the esophagus showed any evidence of intrinsic disease. The mass lay chiefly in front of the trachea but extended posteriorly to press on each lateral wall. The margins of the mass were smooth, except for a slight nodular projection opposite the arch of the aorta. The lower two thirds of the right lung were obliterated by homogeneous dullness. The upper margin of this shadow was convex upward suggesting a mass surrounded by fluid. The heart and mediastinum were markedly displaced to the left, the displacement being out of proportion to the amount of fluid present. The left lung was clear, but there were fine linear areas of density extending outward from both lung roots. Films brought in by the patient taken over a period of two years showed very little change in the appearance of the mediastinal mass.

On the seventh day a right chest tap was done, and 750 cc. of amber blood-tinged fluid was removed. Its specific gravity was 1.010. No tumor cells could be identified in the fluid, and aerobic and anaerobic cultures and a smear were negative for bacteria. An x-ray of the chest taken after the tap showed no evidence of tumor in the right lung.

She was discharged unimproved on the eleventh day.

Last admission (four months later). During the interval her symptoms continued unchanged, and it was necessary for her to have repeated chest taps. She lost about 10 lb. more in weight.

Physical examination revealed a poorly nourished, orthopneic woman. The physical findings were essentially the same as on the previous entry. The blood pressure was 150 systolic, 90 diastolic, and pistol-shot sounds were heard over the brachial and femoral arteries. No enlarged lymph nodes were palpable. There was slight pitting edema of the legs, more marked on the right.

The temperature was 99°F., the pulse 104. The respirations were 25.

The urine examination was negative. The blood showed a red-cell count of 4,400,000 with 80 per cent hemoglobin, and a white-cell count of 3700 with 80 per cent polymorphonuclears.

She was found dead in bed on the evening of the second day. She had been seen two hours previously, and at that time her condition seemed to be as it had been on entry.

X-Ray Interpretation

Dr. George W. Holmes: These films cover a period of a little over six months and show what is described in the text. There is certainly a mass here, and the esophagus is obviously displaced to the left. One might question whether the trachea is actually displaced to the right; it may be, but there is quite a variation in the position of the normal trachea. A mass which displaces the trachea in one direction and the esophagus in the other would have to lie between the two, and one would have to think of an aneurysm. I do not see any indication of that here, however; we have a fairly good view of the aorta, and it does not seem to be dilated or deformed in any way. Aneurysm of a branch of the aorta is certainly rare without some change in the aorta itself. The lesion appears to be noninfiltrating.

Dr. Frederick T. Lord: Where is the x-ray without the fluid?

Dr. Holmes: This shows the area of the tumor mass, and it is pretty free from fluid. There is a lot of fluid at the bases, however.

Dr. Lord: It says in the record: "The trachea was considerably narrowed in the region of the thyroid."

Dr. Holmes: This first film does not seem to show much narrowing of the trachea. The patient had a good deal of radiation and some of these changes may be due to fibrosis. In this second film, however, the trachea is narrowed in the upper portion. The mass lies more anterior than posterior, although it occupies the whole upper part of the chest.

Dr. Aubrey O. Hampton: One of the most interesting features in the case is that the size and shape of the mass have not changed appreciably in two years.

Differential Diagnosis

Dr. Lord: The history suggests an origin in the mediastinum; later there was enlargement which resulted in the tumor that appeared in the neck. The mass did not respond to x-ray in the second instance; it may have in the first. It was probably not a lymphoblastoma. It was almost certainly not a malignant neoplasm originally, but a benign tumor of some sort might have become malignant. Of course the difficulty which arises under such circumstances is to determine the nature of the process. There are many chances. It might be a fibroma, lipoma, chondroma, myoma, cyst adenoma, thymoma or, more plausibly, a substernal goiter. It might be an aneurysm, but the negative Hinton renders this unlikely.

Let us consider for a moment the pleural fluid. The specific gravity of such samples is often of considerable value. This one at 1.010 was low. That is suggestive of a passive transudate rather than an inflammatory process, but it might nevertheless be due to cancer. Some of the fluids secondary to cancer may be low in specific gravity.

This may be a substernal goiter. It is not an aneurysm, from what Dr. Holmes said about the x-ray and because of the negative Hinton test. Echinococcus cyst is a possibility; it cannot be dismissed. Then there is the dermoid, or the teratoma; and I feel confident that if I keep on making this diagnosis I shall eventually be right, according to any system of chances. It is a little suggestive that she had a bronchostenosis because of the practically absent breath sounds at the right base, in spite of the fluid. Fluid does not give absent breath sounds. They may be very much diminished, but they are likely to be bronchial. We do not know whether these were bronchial. I cannot escape the thought that she might have bronchostenosis of the right lower-lobe bronchus.

It is of considerable interest to speculate as to the nature of the fluid. It might be tuberculous, but she had no evidence in the lung of a tuberculous process; it is unlikely. It might be secondary to cancer, or to chronic passive congestion from pressure on the azygos vein. If this is a neoplasm which started as a benign growth and has now become malignant, the chances would seem to be that this fluid is of carcinomatous origin. Do intrathoracic tumors, either benign or malignant, give

rise to pleural fluid by pressure and not always by extension of the growth or metastases? So far as my experience is concerned, pleural fluid in connection with tumors has invariably been due to the latter, so I am disposed to guess that the fluid is of such origin, but it would be of considerable interest to know whether it could follow passive congestion.

In addition to these matters she had hypertension, and a wide pulse pressure — 195 systolic, 80 diastolic. Such a high pulse pressure with a pistol-shot sound over the brachial and femoral arteries is suggestive of aortic regurgitation. The harsh apical systolic murmur suggests mitral insufficiency. The immediate cause of death is hard to explain. She had hypertension. At sixty-two one should think of arteriosclerosis and cerebral hemorrhage or coronary disease. I submit as diagnostic possibilities a mediastinal dermoid or teratoma and carcinomatous pleural effusion.

Dr. Tracy B. Mallory: There is always a wide field for suggestions in these mediastinal tumors. Dr. Churchill, have you anything to add?

Dr. Edward D. Churchill: I saw this patient and know the results of the autopsy, so all I shall add is that I was brave enough to recommend operation at the time of the first admission and to recommend her second admission with a view toward reconsideration of operation which had been refused the first time.

Dr. Lord: What did you think it was?

Dr. Churchill: Our reasoning was a good deal like yours in relation to the chest fluid. We thought that it was suggestive of cancer, but with the long duration of this illness and also that of the pleural effusion we decided that there was a possibility that it could be simply a substernal goiter and that her only chance was to treat it as such and operate through the neck to see if it could be removed. The whole thing might have been due to simple substernal goiter, the picture being confused by the radiation therapy which she had had before we saw her.

Dr. Bernard Jacobson: I think the statement about the diastolic pressure being 80 does not do justice to the situation. We could hear the diastolic sounds going down to about zero, but never heard a diastolic murmur in the heart. At the time when we did not know anything about the diagnosis of the mass we were still puzzled about the accumulation of the fluid. I should like to ask Dr. Lord if he has any other suggestion for the extremely large pulse pressure.

Dr. Lord: I do not know of any relation between pleural fluid and high pulse pressure.

Clinical Diagnoses

Mediastinal tumor.
Pleural effusion, right.
Hypertensive and arteriosclerotic heart disease.

Dr. Lord's Diagnoses

Mediastinal tumor, dermoid or teratoma?
Pleural effusion, secondary to cancer?

Anatomical Diagnoses

Substernal colloid goiter with compression of innominate veins.
Hydrothorax, bilateral.
Pulmonary atelectasis, left.
Pleuritis, chronic fibrous, bilateral.

Pathological Discussion

Dr. Mallory: What we found at autopsy was an extremely large substernal goiter. The entire thyroid was enlarged and was made up of multilobular masses of which one in particular projected down through the suprasternal notch and appeared to press upon the innominate vein and the innominate artery. Histologically, it was a benign colloid goiter. There was virtually nothing else found at autopsy except an effusion. At the time of death there was nearly 3000 cc. of fluid in the right pleural cavity, and about 800 cc. in the left. The heart, in spite of the blood pressure, was practically normal. It weighed only 310 gm., certainly a minimal degree of hypertrophy, and the valves were entirely negative. How this woman's peculiar pulse pressure is to be explained, I have no idea. I was inclined to believe there was enough pressure upon the great veins in the mediastinum to account for the accumulation of fluid.

Dr. Wyman Richardson: Why did she die?

Dr. Mallory: There was no explanation why death should have been so sudden. Her vital capacity must have been reduced. She had nearly 4000 cc. of fluid in the chest. It is only fair to point out that very large amounts of pleural fluid can accumulate within a very few hours, so that that does not necessarily mean negligence when the physician has found no evidence of it. We have seen cases which have been checked by x-ray examination where as much as 4000 cc. of fluid has accumulated within twelve hours.

Dr. Holmes: Did the lungs show any evidence of fibrosis from radiation?

Dr. Mallory: We noticed some fibrosis of the pleural surfaces, but we did not examine them particularly with that in mind, so we may have missed diffuse intrapulmonary changes.

Dr. George W. W. Brewster: Could the goiter

have been removed by operation at any time?

DR. MALLORY: It certainly could have been removed during the first fifteen years, possibly on the first admission.

DR. HOLMES: Do we know how much radiation she had?

DR. JACOBSON: There is some statement about it in the record. She apparently had regression of the substernal goiter after the first x-ray treatment seventeen years previously.

DR. MALLORY: You would not expect x-ray treatment to have much effect on a colloid goiter, I should imagine.

DR. HOLMES: Not if it were colloid. I think it is justifiable to treat if you have a correct diagnosis. If you knew that the patient had intrathoracic goiter and operation were refused or not considered justifiable, the proper amount of radiation to the gland would be considered good treatment; but the trouble in all these cases is that you are never sure of the diagnosis. Radiation may be the wrong thing to do.

CASE 24192

PRESENTATION OF CASE

A seventy-year-old, white, Canadian foreman entered the hospital with the complaint of loss of function of his legs of three weeks' duration.

He was entirely well until three months before entry when he wrenched his back while lifting a crate of eggs. He had a sudden sharp pain localized in his left hip which lasted for a few minutes. He finished his work that day but had difficulty in walking home because of stiffness and soreness in his legs. However, his legs were not numb. These symptoms persisted, and he remained away from work for five weeks. At the end of that time there was only a little residual soreness. Two weeks later, five weeks before entry, he was struck in the side and pinned against a wall by a cart containing twenty-five crates of eggs. The ribs of his right side were damaged but not severely enough to keep him from work. His physician strapped his chest, and in the course of a few days the pain wore off. However, at the time of entry he still had pain in his side when he laughed or coughed. Three weeks before entry he began to have dull pain in the upper lumbar region when he sat down, but which disappeared on walking about. About a week later he began to have a dull heavy feeling in his left foot; in the course of three days this spread to both legs with almost complete loss of their function. If he attempted to stand, his knees buckled under him. There was no pain or coldness in his legs, but they felt heavy and numb, with prickling sensations in the feet. He also had a scalding sensation in the middle of his back when he became overheated, which radiated in a band around his chest. For the week before entry he had involuntary jerking and twitching movements of his legs, which sometimes kept him awake at night. About four days before entry his feet became somewhat swollen. He had no other symptoms of any kind. At the time of entry he was still able to move both legs. He had not lost any weight.

His first wife and two of his siblings had died of tuberculosis about forty years before his present illness. His past history and family history were otherwise negative.

Physical examination revealed a well-developed and nourished man in no apparent discomfort, showing occasional involuntary flexion of his legs. There was marked tortuosity of the retinal arteries, and edema of both lower legs. The general physical examination was otherwise essentially negative. The blood pressure was 170 systolic, 70 diastolic. Neurological examination showed an area of hypesthesia ending at the level of the second lumbar vertebra with absent position and vibration sense in both ankles and feet. Both legs were spastic, and voluntary muscle contractions were weak. The leg reflexes were hyperactive. There was bilateral ankle clonus, and bilateral Babinski signs were present. The examination of the upper part of the body and of the upper extremities was negative. Rectal examination was negative. The prostate felt normal in size and consistence.

The temperature was 98.6°F., the pulse 80. The respirations were 20.

The urine examination was negative. The blood showed a red-cell count of 4,100,000 with 90 per cent hemoglobin and a white-cell count of 10,900 with 69 per cent polymorphonuclears, 26 per cent lymphocytes and 5 per cent monocytes. The serum protein was 7.8 gm. per cent, and the blood Hinton test was negative. A lumbar puncture showed an initial pressure of 50 mm. of water, with respiratory oscillations but without pulse oscillations. Jugular compression elevated the pressure to 60 mm. and abdominal compression elevated it to 210 mm. The lumbar spinal fluid was yellow, contained 1200 mg. per cent of protein, and had a goldsol curve of 0000022553. A cisternal puncture showed an initial pressure of 80 mm., with normal dynamics except for an elevation to only 110 mm. on abdominal compression. The cisternal fluid was clear, contained 12 mg. per cent of protein and 83 mg. of sugar, and had a 0000000000 goldsol curve. The spinal-fluid Wassermann test was negative. X-ray examinations of the spine showed disappearance of the right pedicle of the eighth dor-

sal vertebra. The right side of the body of this vertebra was deformed and less dense than the left side. There was thickening of the soft tissues opposite the least dense area. There was extensive spur formation about the margins of the lumbar vertebrae, and the right twelfth rib showed evidence of an old fracture. Lipiodol injected into the cistern descended to the level of the seventh dorsal vertebra where it met a definite block, the column ending in a pointed extremity. The film showing this also showed partial destruction of the pedicles of the seventh and eighth vertebrae and slight wedging of the body of the eighth.

On the sixth day he began to have abdominal distention and retention of urine. Catheterization yielded 750 cc. of urine. An operation was performed on the thirteenth day.

Differential Diagnosis

Dr. Sumner M. Roberts: The sudden pain in the patient's left hip is perfectly consistent with a back strain. To the layman the hip region includes the whole buttock as a rule, and pain in the buttock, if this is where it was, is a common accompaniment of low-back injuries. Soreness in both legs is not so common following injury, but often there is soreness in both buttocks and upper thighs as the result of a fascial strain of the low back. His improvement under a five weeks' rest is again consistent with a simple strain.

By damaged ribs I suppose they mean broken ribs. We are taught that ribs heal in four weeks, but discomfort after five weeks is not unusual, particularly in an elderly man, and injury to the rib cartilages persists much longer than this.

He had dull pain in the upper lumbar region, which was improved by walking. This is a common story with any mild irritation, infectious or mechanical. The patients feel better while walking about, but they pay for their activity later by stiffening up when they sit down. So far, except for the soreness in both legs, the history suggests nothing unusual that might not happen to any elderly man with a back strain.

Then things began to get serious, and there was rapid loss of power in the legs, with sensory disturbance. The scalding sensation in the mid-back with radiation around the chest is the first sign we have of any trouble higher than the low-back region. His feet became swollen. Does this mean any cardiac or renal condition? Not necessarily. Swelling and edema are common accompaniments of paralysis, especially of the central-nervous-system type. It is particularly common following cerebral accidents.

From the history alone we can tell that he has some lesion in the spinal cord or close to it and pressing upon it, with preliminary symptoms simulating a back strain and possibly aggravated by his crushing injury. Can he have tuberculosis? This can be dormant for some time with a fairly sudden onset of symptoms, and we know that tuberculosis can cause cord compression. This disease is rare at seventy, and all the cases I have seen at this age have had a long history of previous tuberculous trouble in the back. A fresh focus at this age is so unlikely that this diagnosis can be ruled out.

Paget's disease can cause partial collapse of the vertebrae, but seldom, if ever, results in neurologic symptoms. Even if Paget's disease is picked up later on physical examination, I do not think it is the cause of his trouble. Senile osteoporosis can cause the collapse of multiple vertebrae. The symptoms sometimes are very slight and sometimes very severe. Again, however, this condition does not cause cord compression.

The most likely explanation for his symptoms is a tumor of or close to the cord and causing pressure symptoms. His age and previous good health both support this conjecture. The family history of tuberculosis forty years ago does not alter my opinion as to the unlikelihood of this disease's being the cause of symptoms.

The general physical examination was negative. The apparent normality of the prostate is important. Neurological examination suggests trouble at the second lumbar vertebra or a little higher. There was nothing neurological to suggest trouble in the dorsal region or to explain his radiating chest pain. His general good health is against any generalized metastatic lesion, at least involving important organs. The physical examination therefore helps us to localize at least one level of disease in or about the spinal cord, but does not help in making a more detailed diagnosis, and we shall have to depend upon more technical examinations.

His lumbar puncture showed block. The color and chemistry of the fluid confirm this. The lipiodol injection, however, apparently localized the block at the seventh dorsal and not in the upper lumbar region where we rather expected it to be.

The x-rays show a destructive process of the seventh and eighth dorsal vertebrae with thickening of the soft tissues on one side. The destruction is definite, but covers only a small area, and might well have been missed by a less acute examiner. Has he another spinal lesion lower down than the seventh dorsal vertebra? Because of his story of back strain and pain in his hip improving with rest, and because of the sensory disturbance ending

at the level of the second lumbar vertebra, we have had the lumbar region more in mind than the dorsal, which only had one symptom pointing to it. Possibly he has two lesions of a metastatic nature, but the lower lesion is not absolutely necessary. Pressure on the dorsal cord can give leg paralysis without involving the lower trunk or sphincters. This is often seen with tuberculous lesions higher than this. The original hip pain may have been the pain that is sometimes associated with the onset of paralysis due to cord pressure. The ending of the sensory disturbance at the level of the second lumbar vertebra does not fit entirely into the picture, but the definition of sensory levels is not always so accurate as we think it is. Distention and retention of urine simply indicate increasing cord pressure. Operation was done for two purposes — in the hope of relieving cord pressure by laminectomy and for the purpose of biopsy and diagnosis.

We are definitely dealing then with a tumor pressing upon the cord. Is this a metastatic lesion, or is it a primary growth? Two metastatic lesions are common at this age — hypernephroma and carcinoma of the prostate. Hypernephroma is an old-age tumor. The spine is the second most frequently involved region, and the presence of metastases may be the first sign of disease. Carcinoma of the prostate commonly involves the spine, and is again a tumor of old age. This patient, however, shows no signs of general metastasis, as is usually the case, and the x-rays are not typical of metastatic carcinoma. They do not show the multiple mottled areas and increased density one would expect to find with a spreading prostatic lesion.

On a percentage basis alone a metastatic tumor, probably hypernephroma, would seem the best bet. However, I think we have no right to argue that way, but must make our deductions entirely on the evidence at hand. Since there is no evidence of any generalized disease, I should prefer to consider a primary tumor to be the cause of his symptoms. The most likely tumors are fibrosarcoma and a very similar tumor of the same group, a neurogenic sarcoma. Both of these tumors erode bones from without inward. Both of them, when occurring in suitable areas, can be shown to cause soft-tissue shadows. The one thing against them is that lesions in the spine are rare. Fibrosarcoma, therefore, is my diagnosis.

Preoperative Diagnosis

Cord tumor, metastatic?

Dr. Roberts's Diagnosis

Fibrosarcoma.

Anatomical Diagnosis

Plasma-cell myeloma.

Pathological Discussion

Dr. Tracy B. Mallory: That this man suffered from a tumor of, or in the neighborhood of, the spinal cord with secondary pressure upon it was fairly obvious when the findings were all in. The question, of course, concerned the type of tumor. Dr. Roberts has placed his bet upon a primary tumor of a spinal nerve root or the dura, whereas the members of the Neurosurgical Service placed theirs upon a metastatic lesion.

The patient was explored by Dr. Jost Michelsen who did a laminectomy of the sixth, seventh and eighth thoracic vertebrae. He found a soft pinkish extradural tumor about 5 mm. thick which was compressing the cord from the outside at this level. A frozen section was made by Dr. Charles S. Kubik who was able to give an immediate diagnosis of myeloma. Dr. Michelsen, therefore, removed as much of the tumor as he could but did not attempt any radical surgery. Since the tumor seemed to be entirely extradural and the dura was pulsating normally he did not open it.

The subsequent fixed sections of the tumor confirmed the diagnosis of plasma-cell myeloma. The tumor is made up almost entirely of rather small, round cells with eccentric round nuclei showing the typical cartwheel distribution of the chromatin. As is often the case, many of the cells contain two and three of these nuclei. Following operation the patient was referred to the X-Ray Department for treatment. He received 2400r in eight 300-r doses, but failed to show any improvement in his symptoms. Perhaps Dr. Hampton will say a word in regard to the treatment.

Dr. Aubrey O. Hampton: The treatments were given through an 8 by 10 cm. field, centered over the eighth dorsal vertebra, and were completed twenty-two days after the operation. The patient has not been observed since that time.

Some cases of plasma-cell myeloma are quite sensitive to radiation, but many others show very little response. This patient is probably in the latter group.

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PURE FOOD, DRUG AND COSMETIC BILL

The House Committee on Interstate and Foreign Commerce has reported favorably a highly undesirable bill for the control of foods, drugs and cosmetics—a bill so bad with regard to method of enforcement that it ought to be entitled "a bill to perpetuate impure foods, drugs and cosmetics." In it, great ingenuity has been shown in making the legal processes so complex and devious that it will be very difficult to get satisfactory enforcement and almost impossible to obtain quick action on any food, drug or cosmetic that is likely to cause serious disease or even death.

The bill is so impracticable in this feature that the Secretary of Agriculture has written a statement including these vigorous words:

> If a bill containing this provision were enacted, it would not constitute any material contribution to the public protection that the department cannot now extend under the existing law. In some respects it would afford even less protection than that afforded by the existing law, which is broad and general in its terms and is to some degree applicable and effective in the fields covered by the sections involved in this discussion.
>
> It is the department's considered judgment that it would be better to continue the old law in effect than to enact Senate 5 with this provision.
>
> I am of the opinion that if Section 701 (f) remains in the bill its effect would be to hamstring its administration so as to amount to a practical nullification of the substantial provisions of the bill.
>
> If there is to be exploration into new fields of administrative law, may I urge that it not be in the field of vitally important public-health legislation.

The above is quoted from the minority report of the House Committee on Interstate and Foreign Commerce, which was signed by six of its members. (It is pleasing to us that the Honorable Pehr G. Holmes, of Worcester, Massachusetts, the only New England member of this committee, signed this minority report.)

In the minority report the following sentence also appears:

> Weighing the advantages and disadvantages for the protection of consumer welfare presented by the terms of this bill, we are unable to escape the conclusion that because of the extraordinary provision for court review of regulations in Section 701 (f), which would postpone indefinitely the consumer protection that can now be afforded in some degree by the present law in much of the field to be covered by these regulations, it would be better to continue the old law in effect than to enact Senate 5 with this provision.

It would be to the advantage of the medical profession and lay public to have this present house bill (Senate 5, Report No. 2139: Union Calendar No. 770) defeated unless these objectionable features are eliminated. The original bill as passed by the Senate on March 9, 1937, is greatly to be preferred to the bill as amended in House committee. If the former cannot be passed, then no bill is greatly to be desired: this would leave legislation on pure foods and drugs in its existing form.

Physicians in New England can help to right a bad situation, if they write promptly to their senators and representatives protesting against the ac-

tion of the committee as outlined above and asking a vote against this bill, unless the section dealing with enforcement be restored to the form contained in Senate 5, as already passed by the Senate.

JOSIAH MACY, JR., FOUNDATION

The Josiah Macy, Jr., Foundation in a recent release reports in a six-year review that from its incorporation until December 31, 1936 it has made three hundred and twenty-four grants totaling $806,681.75. These grants have been made to thirty-four different universities and twenty-seven other agencies of research in the United States, Belgium, Czechoslovakia, France, Germany, Hungary, Netherlands and U. S. S. R.

Dr. Ludwig Kast, president of the Foundation, stresses in his foreword to the report the necessity of preserving the unity of the patient as a psychosomatic entity. In the long run, he believes, the effectiveness of any planning depends upon free and enlightened progress within the medical profession. With the increasing number of processes and reactions to be observed and evaluated and the ever-enlarging number of specialists required to observe and evaluate them, the task of adequate diagnosis and effective health care requires a concern for the patient as an individual personality and the sympathetic insight that the family physician of old was able to offer.

There is, moreover, a great need for the further study of growth, development, maturation and aging, not only as a medical problem but as a social and economic one. The trend is now toward the elimination of the older worker from employment, not only because he cannot sustain the pressure of modern occupations, but also because of the availability of younger men and women for a limited if not, indeed, a rapidly diminishing supply of jobs. This situation, it is believed, will give rise to emotional conditions which must find some release and which, in the older group, will probably be expressed in mental and psychosomatic disorders. This — the health care of the aging individual — is one of the most severely challenging medical, social and economic problems that must be faced in future years.

MASSACHUSETTS MEDICAL SOCIETY

GOLF TOURNAMENT

Due to the fact that there has been so much demand for a Golf Tournament to be held in connection with the annual meetings, the Committee of Arrangements has planned to hold one at the Commonwealth Country Club, 91 Algonquin Road, Newton Center, on Wednesday afternoon, June 1.

One group will consist of those members who hold either state or club handicaps, while a Kickers Tournament has been arranged for those who have no handicaps. A trophy, the Massachusetts Medical Society Golf Challenge Cup, presented by one of the members, will be awarded for the low net score; this must be won three times to obtain permanent possession. Other suitable prizes have been secured for net and gross scores in both divisions.

The details of the tournament itself will be attended to by Mr. John Corcoran, of the Massachusetts Golf Association, thus assuring efficient management.

It is hoped by many of the members that a permanent golf organization may be formed within the Society, and some action will undoubtedly be taken during or following the tournament.

PROPOSED AMENDMENTS TO THE BY-LAWS

Due to a typographical error in the pamphlet announcing proposed amendments to the by-laws, Amendment No. 7 reads "Chapter VII, Section 2." This should have read "Chapter VII, Section 11."

Alexander S. Begg, *Secretary*.

SECTION OF OBSTETRICS AND GYNECOLOGY

M. Fletcher Eades, M.D., *Secretary*
19 Bay State Road
Boston

Case History No. 71. Low-Attached Placenta at Term

Mrs. V. D., a twenty-five-year-old multipara, was admitted to the hospital on February 7, 1938, for induction.

The family history was negative and her past history was not important except for a moderately severe attack of pyelitis four weeks after her last confinement in 1936. Catamenia began at thirteen, were regular every twenty-eight days,

A series of selected case histories by members of the section will be published weekly.

Comments and questions by subscribers are solicited and will be discussed by members of the section.

and lasted four or five days. There had been two previous normal pregnancies. Her last period was April 22, 1937, making her due for delivery on January 29, 1938.

The prenatal course was normal throughout. She was seen at regular intervals of three weeks.

Upon physical examination at admission she was found to be a well-developed and nourished woman. The lungs were clear and resonant; there were no rales. The heart was not enlarged, and there were no murmurs. The blood pressure was normal. The uterus was enlarged to a size consistent with her dates. The urine was free of albumin. As the patient had gone ten days over term, induction was decided upon. When the patient entered the hospital the evening before induction was planned, she was completely symptom free. She was put to bed after a perineal preparation had been done and promptly went to sleep.

At 2 a. m., five hours after admission, the patient called the nurse and said that her membranes had ruptured. On examination the nurse found the bed soiled with bright-red blood, sufficient to make a stain 30 cm. in diameter. The attending obstetrician was called and found the patient in good condition: the blood pressure was 120 systolic, 70 diastolic; the pulse 90; the fetal heart tones regular, at a rate of 140. The fundus was soft, and there was a small amount of bright-red flow from the vagina. A tentative diagnosis of partial separation of the placenta was made. Immediate grouping of the patient's blood was done, and compatible donors were on hand in case of need.

One-quarter grain of morphine was given, and an abdominal binder was firmly placed over the fundus. The patient was then brought to the delivery room where a careful vaginal examination was done under routine precautions. The cervix was two-fingers dilated, soft and nearly completely taken up. Careful examination of the lower segment revealed no placenta and confirmed the diagnosis of separation. The vertex was fitting into the inlet with some forebag, and rupture of the membranes to stimulate labor was decided upon. About 200 or 300 cc. of clear amniotic fluid escaped after puncture of the membranes. To take up the slack after the fundus had decreased in size an additional binder was put over the first one to insure its being held securely and to cause pressure on the cervix. Labor began in about half an hour and progressed steadily. The cervix was fully dilated two and a half hours later, and after one hour of ineffectual second-stage labor a low mid-forceps was done, the head being posterior on the right and somewhat extended. A healthy male child weighing 8 lb., 8 oz., was delivered. Pituitary solution, 1 cc., was given intramuscularly; the fundus reacted well, and the placenta was expressed fifteen minutes after the delivery of the child. There was no unusual flow after the third stage, the fundus remaining firm with no need of further stimulation. The placenta was examined carefully and one-third of the outer margin, to a depth of 1 cm., showed evidence of separation. This apparently was the lower margin since it was nearest the point of rupture on the membranes. The postpartum convalescence was uneventful.

Comment. Because a patient has gone ten days over the expected date of delivery is no real reason for induction. The time of induction should always be based upon the condition of the cervix. Had this patient been examined before she went into the hospital, it would have been determined that the cervix was ready for labor. Many cases ten days before the computed day of labor are not ready to have a baby, as is determined by vaginal examination, which fails to show an obliterated and open cervix. The amount of external bleeding would lead one to infer that a partial separation of a low-attached placenta was the cause of the hemorrhage. It is uncommon to have a large amount of external bleeding when a normally situated placenta becomes separated. A vaginal examination is the only way to determine specifically the source of the bleeding. In this case no placenta was felt, and the diagnosis of partial premature separation was made. The treatment was ideal. As it is not stated that the patient was definitely in labor, it is fair to infer that she was not in labor; the vaginal examination which showed the cervix to be dilated two fingers is perfectly compatible with the physiologic change that occurs late in pregnancy. The separation of a low-attached placenta is undoubtedly the commonest cause of bleeding in cases that are close to term.

GREEN LIGHTS TO HEALTH

SPONSORED BY THE MASSACHUSETTS MEDICAL SOCIETY AND THE MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COURTESY WAAB — WEDNESDAYS, 8:15 P. M.

May 18 — Epilepsy. William G. Lennox.
May 25 — Scurvy — Infantile. Richard C. Eley.
June 1 — Nose and Throat. Charles T. Porter.
June 8 — Tuberculosis. Frederick T. Lord.
June 15 — Medical Ethics. David Cheever.
June 22 — Fads in Medicine. Shields Warren.
June 29 — Diabetes. Reginald Fitz.

DEATH

MORROW — CHARLES H. MORROW, M.D., of Gloucester, died May 2. He was in his seventy-eighth year.

A native of Gloucester, he received his medical degree from the University of Pennsylvania School of Medicine in 1885, went to Gloucester shortly afterward and practiced there for fifty-three years. Dr. Morrow was at one time on the staff of the Addison Gilbert Hospital. He was a fellow of the American Medical Association and

of the Massachusetts Medical Society and a member of the Masonic Order.

MISCELLANY

PETER BENT BRIGHAM HOSPITAL ANNIVERSARY

On May 5, 6 and 7 a celebration of the twenty-fifth anniversary of the opening of the Peter Bent Brigham Hospital for the reception of patients was held at the hospital in conjunction with a reunion of graduates of the professional and nursing services of the hospital.

On each of the three days up to 10:30 a. m. various hospital demonstrations, ward visits and surgical operations were conducted. After this there was a program of scientific and nursing papers, — more than one hundred in number, — presented by graduates and present members of the hospital professional and nursing staff.

On the forenoon of May 7 there was a very large public meeting at which the Rt. Rev. William Lawrence, Bishop Emeritus of the Episcopal Diocese of Massachusetts, gave the invocation; His Excellency Charles F. Hurley, Governor of the Commonwealth, gave the "Greetings of the State"; His Honor Maurice J. Tobin, Mayor of Boston, the "Greetings of the City of Boston"; Dr. Dean Lewis, first surgeon-in-chief pro tempore of the Peter Bent Brigham Hospital, surgeon-in-chief of the Johns Hopkins Hospital, the "Greetings of the Medical Profession," and President James B. Conant, Harvard University, the "Greetings of the University." Dr. Henry A. Christian, physician-in-chief of the Peter Bent Brigham Hospital and Hersey Professor of the Theory and Practice of Physic in the Harvard Medical School, made an address entitled "A Hospital Comes to Town: The story of the Peter Bent Brigham Hospital in Boston"; Dr. Elliott C. Cutler, surgeon-in-chief of the Peter Bent Brigham Hospital and Moseley Professor of Surgery in the Harvard Medical School, an address entitled "A Surgeon Looks at the Record"; and Dr. C. Sidney Burwell, physician at the Peter Bent Brigham Hospital and dean of the Faculty of Medicine of Harvard University, one entitled "The Future of the Hospital." The benediction was pronounced by the Rt. Rev. Francis L. Phelan, chancellor of the Archdiocese of Boston. These exercises were followed by a luncheon on the hospital grounds for all invited guests.

On each afternoon of these three days, tea was served on the hospital lawn. On the evening of May 5 a musical comedy was given at the hospital by the resident professional staff. On the evening of May 7 there was a dinner for four hundred at Vanderbilt Hall, Harvard Medical School, followed by a dance at Longwood Towers, Brookline. At all these events of the celebration the graduates were the guests of the trustees of the Peter Bent Brigham Hospital.

FOURTH ANNUAL RURAL HEALTH CONSERVATION CONTEST

In the Rural Health Conservation Contest, conducted annually by the Chamber of Commerce of the United States in co-operation with the American Public Health Association, the winner for 1937 in the Northeastern Division was recently announced to be Columbia County, New York, and awards of merit go to Barnstable County, Massachusetts; Saginaw County, Michigan; Southern Berkshire District, Massachusetts; Cortland County, New York; Mecosta-Osceola Health Unit, Michigan; Richland County, Ohio; and Ottawa County, Michigan.

Some of the points considered by the committee of health experts entrusted with making the awards are: (1) the extent to which the water supply is protected; (2) the point at which sanitation has advanced in rural homes; (3) the safety of the milk supply; (4) adequate care of prenatal cases; (5) medical supervision of infants; (6) the availability of well-trained nursing service; (7) the degree in which local physicians and dentists aid in the public-health program; (8) activities to control tuberculosis and syphilis.

NOTICES

BOSTON CITY HOSPITAL

There will be a symposium on traumatic surgery in the Thorndike Amphitheater, Boston City Hospital, on Saturday, May 21, at 10:30 a. m.

Bone and Joint Injuries. Dr. Otto J. Hermann.
Abdominal Injuries. Dr. William R. Morrison.
Pathology of Brain Injuries. Dr. Timothy Leary.
Clinical and Surgical Aspects of Brain and Spinal Cord Injuries. Dr. Donald Munro.

CHARLES M. GREEN, M.D., *Chairman*,
Committee on Hospital Clinics.

TRUDEAU SOCIETY

The annual meeting of the Trudeau Society will be held at the Middlesex County Sanatorium, Trapelo Road, Waltham, on Tuesday, May 17, at 4:00 p. m.

PROGRAM

The State's Experience with Silicosis. Mr. Manfred Bowditch.
Results in a Series of Internal Pneumonolyses using Electrosurgery. Dr. Harlan F. Newton.
Bronchial Complications among Tuberculous Patients. Dr. Lowrey F. Davenport.
Spontaneous Pneumothorax: A suggestion for the treatment of acute symptoms. Dr. Francis P. Dawson.

MOSES J. STONE, M.D., *Secretary*.

CARNEY HOSPITAL

Clinical exercises in observance of the seventy-fifth anniversary of the founding of the Carney Hospital, under the direction of the Sisters of Charity, will be held on Tuesday and Wednesday, May 17 and 18.

PROGRAM

TUESDAY

9:15 a. m. — Operations.
First Surgical Service, Dr. A. McK. Fraser.
Gynecological and Obstetrical Service, Dr. L. E. Phaneuf.
Urological Service, Dr. Roger C. Graves.
10:00 to 11:30 a. m. — Medical ward rounds, Dr. L. F. Curran and associates.
2:00 to 4:45 p. m. — Series of short papers will be read by various members of the several services at the hospital.

WEDNESDAY

9:15 a. m. — Operations.
Second Surgical Service, Dr. W. E. Browne.
Orthopedic Service, Dr. W. R. MacAusland.

10:00 to 11:30 a. m. — Medical ward rounds, Dr. L. F. Curran and associates.
2:00 to 4:45 p. m. — Series of short papers.
8:15 p. m. Dr. Henry A. Christian will read a formal paper "Glomerular Dominance in Bright's Disease." This meeting will be held at John Hancock Hall, 90 St. James Avenue, Boston.

Members of the medical profession are cordially invited to attend these exercises. Further information concerning this program can be obtained by calling SOU 2070.

WILLIAM E. BROWNE, M.D., *Secretary*,
Advisory Board, Carney Hospital.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The annual meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday evening, May 18, at 8 o'clock.

The council will meet at 6:00, and the informal dinner will be held at 6:30.

PROGRAM

Reports of officers and committees.
Election of officers.
Address: After-Treatment of Poliomyelitis. Dr. Kristian G. Hansson, director of physical therapy, New York Hospital.

All members of the medical profession are cordially invited to attend.

WILLIAM D. MCFEE, M.D., *Secretary*.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

The next meeting of the Boston Society of Psychiatry and Neurology will be held at the Boston Medical Library, on Thursday evening, May 19, at 8:15.

PROGRAM

Intracranial Aneurysms. Dr. C. A. McDonald and Mr. Milton Korb.
The Vascular System of the Human Spinal Cord. Dr. T. H. Suh.
A Method of Measuring Consciousness in Petit-Mal Epilepsy. Dr. R. S. Schwab.
A Case of Mucous Colitis: Its psychiatric manifestations. Dr. M. Yorshis.

H. HOUSTON MERRITT, M.D., *Secretary*.

NEW ENGLAND PATHOLOGICAL SOCIETY

The annual meeting of the New England Pathological Society will be held at the University Club, Thursday, May 19, at 6:30 p. m.

Dr. Robert A. Moore of Cornell University Medical College will speak on "Benign Enlargement of the Prostate."

J. B. HAZARD, M.D., *Secretary*.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, MAY 16

TUESDAY, MAY 17

*Clinical exercises in observance of the seventy-fifth anniversary of the founding of the Carney Hospital.
*9-10 a. m. Boston Dispensary. Pathogenic Fungi. Dr. Jacob Swartz.
9:30 a. m. Massachusetts General Hospital. Thoracic clinic. Ether Dome.
*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.
*12 m. South End Medical Club. Headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

WEDNESDAY, MAY 18

*Clinical exercises in observance of the seventy-fifth anniversary of the founding of the Carney Hospital.
8 a. m. Massachusetts General Hospital. Grand rounds. Orthopedic Department.
*9-10 a. m. Boston Dispensary. Hospital case presentation. Dr. S. J. Thannhauser.
12 m. Boston Society for the Advancement of Gastroenterology. Cheever Amphitheater, Boston City Hospital.
*12 m. Clinicopathological conference. Children's Hospital amphitheater.
*8 p. m. New England Society of Physical Medicine. Hotel Kenmore.

THURSDAY, MAY 19

8 a. m. Massachusetts General Hospital. Circulatory clinic rounds.
*9-10 a. m. Boston Dispensary. Erythema Nodosum. Dr. George E. Currier.
11 a. m. Massachusetts General Hospital. Medical grand rounds.
12 m. Massachusetts General Hospital. Clinicopathological conference.
6:30 p. m. New England Pathological Society. University Club.
8:15 p. m. Boston Society of Psychiatry and Neurology. Boston Medical Library.

FRIDAY, MAY 20

*9-10 a. m. Boston Dispensary. Hemolytic Streptococcal Infections, Factors of Significance in Prognosis and Treatment. Dr. Chester S. Keefer.
10 a. m. Massachusetts General Hospital. Fracture rounds.
*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

SATURDAY, MAY 21

*9-10 a. m. Boston Dispensary. Hospital case presentation. Dr. Thannhauser.
*10 a. m. - 12 m. Staff rounds at the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

*Open to the medical profession.

MAY 12 — National Hospital Day. Page 788, issue of May 5.
MAY 16 and 17 — American Neisserian Medical Society. Page 582, issue of March 31.
MAY 17 — South End Medical Club. Page 788, issue of May 5.
MAY 17 — Trudeau Society. Page 825.
MAY 17 and 18 — Clinical exercises in observance of the seventy-fifth anniversary of the founding of the Carney Hospital. Page 825.
MAY 18 — Brookfield Medical Club. Page 788, issue of May 5.
MAY 18 — Boston Society for the Advancement of Gastroenterology. Page 788, issue of May 5.
MAY 18 — New England Society of Physical Medicine. Notice above.
MAY 19 — New England Pathological Society. Notice above.
MAY 19 — Boston Society of Psychiatry and Neurology. Notice above.
MAY 21 — Boston City Hospital. Symposium on Traumatic Surgery. Page 825.
MAY 31, JUNE 1 and 2 — Annual meeting of the Massachusetts Medical Society. Hotel Bradford, Boston.
JUNE 1 and 2 — National Society for the Advancement of Gastroenterology. Page 746, issue of April 28.
JUNE 6, 7, 8, and 9 — American Association of Industrial Physicians. Page 499, issue of March 17.
JUNE 10 and 11 — American Heart Association. Page 707, issue of April 21.
JUNE 13-17 — American Medical Association. San Francisco.
JUNE 13, OCTOBER 8 and NOVEMBER 15 — American Board of Ophthalmology. Page 282, issue of February 10.
JUNE 23 — Pentucket Association of Physicians. Hotel Bartlett, 95 Main Street, Haverhill, 8:30 p. m.
SEPTEMBER 12-14 — American Association for the Study of Goiter. Page 545, issue of March 24.
OCTOBER 17-21 — Clinical Congress of the American College of Surgeons, New York City.
OCTOBER 24-26 — Academy of Physical Medicine, Scientific Session. Washington, D. C.

DISTRICT MEDICAL SOCIETIES

HAMPDEN

Meeting will be held on the fourth Tuesday in July.

PLYMOUTH

Meetings will be held at 11 a. m. on May 19 and July 21.